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A.M.A. ARCHIVES OF

INTERNAL MEDICINE

Isoniazid After Five Years

The Anatomy Acts of 1831 and 1832
Norman M. Keith and Thomas E. Keys

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Eddy D. Palmer

Bacterial Shock
Joseph A. Ezzo and William A. Knight Jr.

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An Evaluation of Lymphadenopathy in Systemic Disease
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The Treatment of the Nephrotic Syndrome with Steroids in Children and Adults
Kurt Lange, Ruth Strang, Lawrence B. Slobody, and Eugene J. Wenk

Cause of Death in Ruptured Intracranial Aneurysms
Jose Bebin and Robert D. Currier

Syphilis
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James A. Kemp

Hypotensive Reaction Following the Use of Glucagon
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Eosinophilic Leukemia
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A. M. A.
ARCHIVES OF INTERNAL MEDICINE

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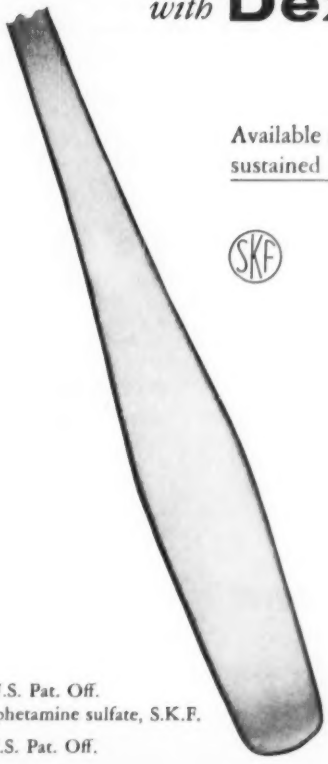

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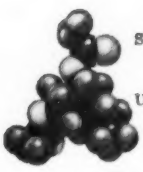

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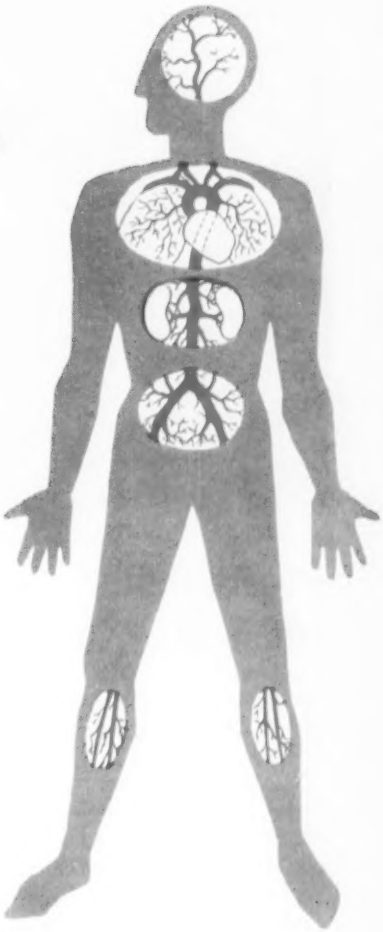

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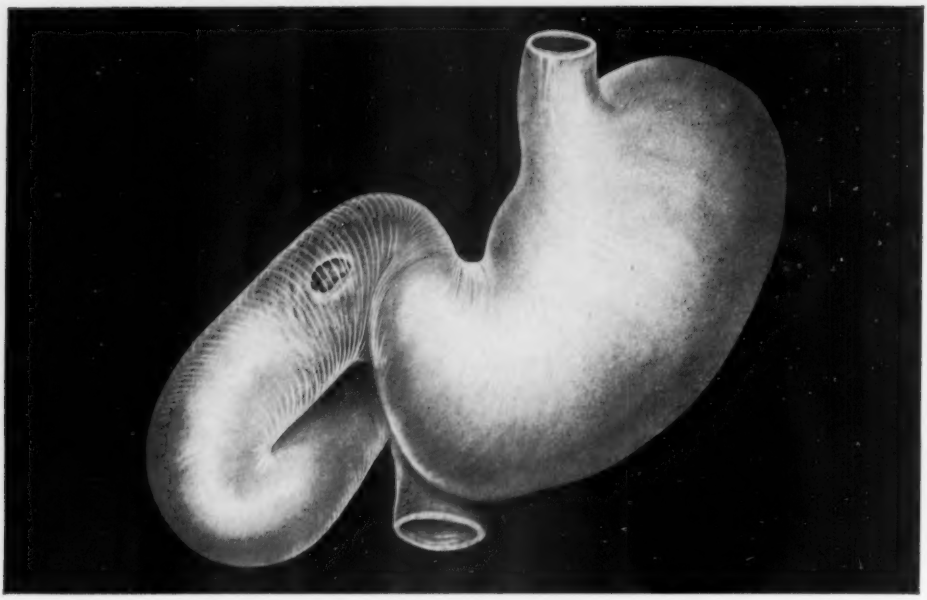

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Editorials

Isoniazid After Five Years

It is somewhat less than five years since the first publications on isoniazid appeared in April, 1952,[1-6] but this drug had then been under clinical investigation by two groups for more than half a year.[5,6] It is possible, therefore, to look back on a full five years of clinical experience.

The marked symptomatic benefit noticed and resulting conspicuous exuberance displayed by many of the patients first to receive the isonicotinic acid hydrazides followed more often from iproniazid than from isoniazid.[7] Because of its lower toxicity and its equal, or very nearly equal, objective benefit, isoniazid itself has virtually displaced the isopropyl derivative. Its less dramatic, and perhaps somewhat slower effect caused some disappointment when isoniazid became generally available. An even more disturbing factor, however, was the in vitro demonstration of relatively early increased bacterial resistance in successive cultures of sputum. It was then expected by many clinicians and microbiologists that in vitro resistance and loss of therapeutic effect would be as closely correlated as had been the case with streptomycin. Shortly after the introduction of streptomycin such correlations had been conclusively demonstrated, and the levels of significant resistance could be clearly, if perhaps not critically, defined. Several early reports of isoniazid treatment in pulmonary tuberculosis suggested that similarly close correlations were to be found and that isoniazid might lose clinical efficacy even more rapidly than streptomycin. These early reports, however, were not conclusive, and they have not been confirmed more recently. From the beginning a more consistently favorable clinical course was observed in isoniazid-treated miliary tuberculosis than had been seen with streptomycin. Relapse of this acute generalized form under isoniazid treatment was reported early to be rare,[8] in contrast to streptomycin. Subsequent experience has confirmed the correctness of these early observations. The superiority of isoniazid over streptomycin in this respect has a bearing on the problem of bacterial resistance which was overlooked by many at the time but which, in the first year of isoniazid experience, foretold what has lately become increasingly apparent, that bacterial resistance to isoniazid is a factor of relatively small clinical importance. The present situation is indicated in the recent report of Fox and Sutherland,[9] who,

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From the Department of Medicine, Cornell University Medical College, and the New York Hospital, New York, N. Y.

on the basis of a careful study of 234 patients with pulmonary tuberculosis, could not show clinical disadvantages due to isoniazid resistance and could correlate the emergence of isoniazid-resistant organisms in the sputum only with the extent of initial cavitation. Others have found not only a lack of correlation between clinical progress and in vitro susceptibility tests, but an absolute incidence of clinical deterioration under long-term isoniazid treatment which is not significantly higher than with two-drug regimens,[10,11] under which the emergence of in vitro resistance is demonstrably reduced.

In the long-term therapy of pulmonary tuberculosis, isoniazid, without any companion drug and despite declining drug susceptibility in successive sputum cultures, is about as effective as the old streptomycin-PAS combination.[10,12] It is, to be sure, not demonstrably superior, and if isoniazid could be used only in this way, it might be considered to have added little except for its lower toxicity and its much greater practicability. When isoniazid is administered concurrently with either streptomycin or PAS, however, the results are appreciably better than with streptomycin and PAS.[12-14] The administration of all three drugs simultaneously appears to add no further measurable benefit. A daily rather than a twice-weekly administration of streptomycin in conjunction with daily isoniazid appears to be the optimal regimen.[14] This is universally recognized, at least tacitly, as it is the agreed-upon regimen for the most dangerous forms of tuberculosis, namely, the miliary and meningeal. In chronic pulmonary tuberculosis some prefer to use PAS with isoniazid in order not to risk the development of bacterial resistance to both of the two major drugs.

Such regimens in which isoniazid is paired with another drug, particularly streptomycin or PAS, were originally devised to delay bacterial resistance, especially to isoniazid. Their apparent superiority, in terms of roentgenologic improvement and reversal of infectiousness, to isoniazid by itself is due probably less to this factor, however, than to others. A mutual enhancement of isoniazid and streptomycin by each other has been demonstrated.[15] Such an enhancement is also found between isoniazid and pyrazinamide, a combination which is even more effective in vivo as demonstrated experimentally.[16] Clinically the pyrazinamide-isoniazid treatment appeared for a time to be most promising, until the hepatic toxicity of pyrazinamide proved to be prohibitive.[17] Regimens of isoniazid paired with such less important drugs as viomycin or cycloserine have not yet been extensively investigated, but will probably not prove of importance for initial therapy because of the considerable toxicity and limited efficacy of these agents.

It has been reported by two groups of investigators that PAS, when given concurrently with isoniazid, reduces the acetylation of the latter.[18,19] The relative superiority of isoniazid-PAS over isoniazid alone, which is statistically significant but not marked,[12] may be largely due to this factor. By blocking the partial inactivation by acetylation, which varies in degree between different persons, the PAS effect may be equivalent merely to giving larger doses of isoniazid. It also has been shown that the hitherto safe limit of dosage of isoniazid of approximately 5 mg. per kilogram of body weight per day can be raised at least to some extent if pyridoxine is given concurrently to protect against neurologic toxicity.[20,21] Interference by pyridoxine with the antituberculous action of isoniazid is thought not to occur to an appreciable extent. High-dose isoniazid therapy, with this pro-

tection, is under continued investigation, but the safe limit for sustained therapy is not yet established.[22]

While these important studies are being pursued, the search continues for a more bactericidal agent, or one which in combination with isoniazid or with the other drugs mentioned may be eradicative in vivo. Pyrazinamide-isoniazid very nearly achieves eradication in the mouse, and there appears to be no theoretical reason why an eradicative therapy should not eventually be devised.

Dissemination of primarily drug-resistant infection widely throughout the population has been feared, and this may be an actual danger. However, Chaves and his co-workers have recently found only 0.5% cultures from newly diagnosed patients resistant to streptomycin and only 0.8% resistant to isoniazid.[23] In the year 1955 there was no significant increase in the incidence of primarily drug-resistant infections over 1953 and 1954.

Early failure of response to isoniazid, in severely ill patients, or to isoniazid reinforced by streptomycin, does not necessarily, or even probably, mean a primarily drug-resistant infection. That it does not is illustrated by the following case.

The patient is a 43-year-old Negro woman who had been ill with bilateral tuberculous pneumonia for only three weeks prior to the initiation of treatment with isoniazid alone, in the high dosage of 10 mg. per kilogram per day. This was a regimen then under investigation, but because of the patient's critical condition, she was removed after three days from the experimental series, and a conventional regimen was substituted of isoniazid, streptomycin, and PAS, in standard doses. The patient did not improve with this or when the isoniazid dose was again raised. Her general condition deteriorated alarmingly following an exploratory laparotomy on the 20th hospital day. This was performed because of severe abdominal symptoms and a suspected pyogenic complication. By the 32d day her condition was grave, with extreme weakness, tachycardia, and tachypnea. Corticotropin therapy was now begun, and after eight hours there was a dramatic remission of all of the symptoms. The steroid therapy was maintained for 37 days, but tapered before final withdrawal. The subsequent course has been entirely satisfactory, not alone symptomatically, but bacteriologically and roentgenologically. Isoniazid and streptomycin therapy have been maintained.

The use of steroid hormones in this manner in fulminating tuberculosis infection, which might clinically appear to be drug-resistant, is as yet little documented in the American literature, apart from the use of these hormones in tuberculous meningitis. There is a growing recorded experience in Europe of the concurrent administration of steroids with antimicrobial therapy in various other forms of acute tuberculosis. Apparent activation of the antimicrobial therapy as in the present instance has been occasionally noted by Even and his co-workers,[24] and by others, as well as an almost uniform acceleration of clinical improvement. The present case is not an isolated instance in our own service,[25] and similar results in fulminating tuberculosis have been communicated to us from other clinics. A small but impressive series was presented recently by Lambert.[26]

It is difficult yet fully to assess the effect of isoniazid on the general tuberculosis mortality because prior to its introduction this was already sharply declining, particularly since the start of the antimicrobial era.[27] Isoniazid has, however, without question changed the results in miliary and meningeal tuberculosis from mediocre to good. This is in part due merely to the better diffusion of isoniazid into the central nervous system. Most probably it is due also to other factors, particularly the lower inactivation of isoniazid in vivo by bacterial drug resistance

than occurs with streptomycin. If this is true it may be expected that a further impetus, attributable specifically to isoniazid, on the declining mortality and morbidity of tuberculosis will become clearly detectable as the statistics of successive years accumulate. The suppressive effect on the spread of the disease may be greater than can yet be appreciated.

In conclusion, it appears at the end of five years that isoniazid has attained predominant importance in the therapy of tuberculosis and that it has fulfilled its early promise to any who viewed this realistically.

CARL MUSCHENHEIM, M.D.
133 E. 64th St., New York

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The Anatomy Acts of 1831 and 1832

A Solution of a Medical Social Problem

NORMAN M. KEITH, M.D., and THOMAS E. KEYS, M.A., Rochester, Minn.

Community life in New England and Great Britain 120 years ago was undergoing change. The industrial revolution and recovery from the Napoleonic wars had created new political, social, and educational situations. New knowledge regarding science and economics was increasing rapidly, and, at the same time, political and social horizons were widening. The public demanded solutions of pressing problems. To ease the serious political unrest, parliamentary reforms were urgently needed, and liberal leaders came forward with remedial legislation. Medicine also was challenged by the awakening.

At the time, study of human anatomy was seriously restricted. Antiquated laws supported the prejudice of the public against dissection. Discussions between representatives of the medical profession and the public suggested the necessity of legislative action. In this communication we hope to transmit some of the atmosphere of controversy which permeated a bygone age of political and social upheaval.

The Problem

During the period 1820 to 1835 the teaching of medicine became increasingly important both in Great Britain and the United States. There were demands for more and better-trained practitioners, and many alert young men were attracted to the profession. As is evident in several studies of the historical aspects of the problem,[1-8] those in authority recognized that study of human anatomy, and particularly knowledge gained in the course of dissection of the human body, was basic to medical and surgical practice. Yet the student encountered a curious paradox: The surgical fraternity was especially jealous of the standards of anatomic knowledge and, in association with the legal profession, advocated that severe penalties be imposed on incompetent surgeons. But the obvious remedies—legalizing dissection of the human body and increasing the opportunities for such dissection—were not sufficiently invoked, and many impediments remained in the path of the medical student.

This is not to say that sturdy effort to remove the difficulties was lacking.[9,10,67] In Massachusetts (Fig. 1)[9] and in Great Britain (Fig. 2)[67] excellent memoranda were compiled; their essential agreement is remarkable. Investigators of the problem in both regions recognized the general rise of intelligence and the increase in breadth of education that was taking place in their communities. They also realized that outmoded laws and popular prejudices should not hinder the study of human anatomy.[11]

The "Resurrectionists" and "Burking"

Historians now agree that William Hunter was as famous as his brother John, and William is credited with reform in the teaching of anatomy. In 1747 he established complete courses in anatomy, and these included many dissections in which the students participated. By 1793, according to Parsons,[12] there were 200 regular students of anatomy in London alone, but, in 1823, there were about 1,000.

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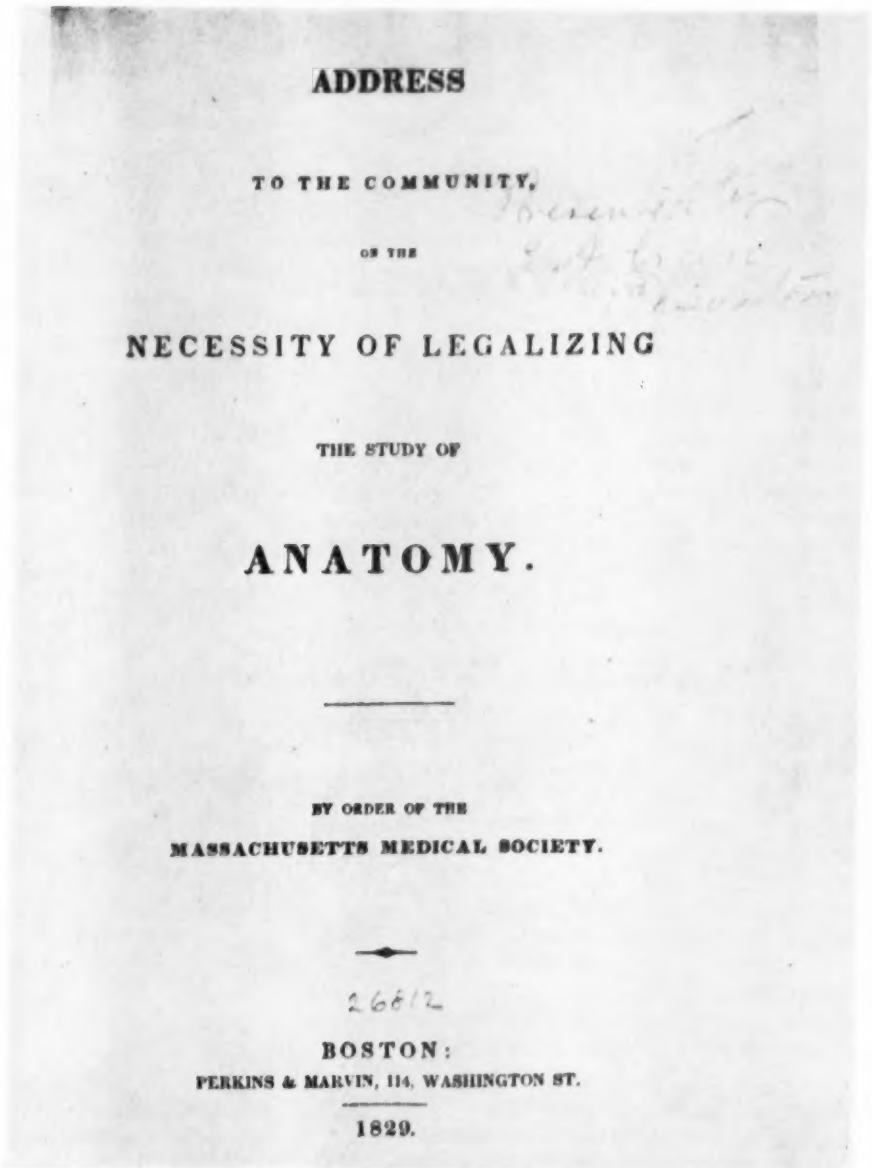
Emeritus Member, Section of Medicine (Dr. Keith), and Librarian (Mr. Keys), Mayo Clinic.



ADDRESS

TO THE COMMUNITY,

ON THE

NECESSITY OF LEGALIZING

THE STUDY OF

ANATOMY.

BY ORDER OF THE

MASSACHUSETTS MEDICAL SOCIETY.

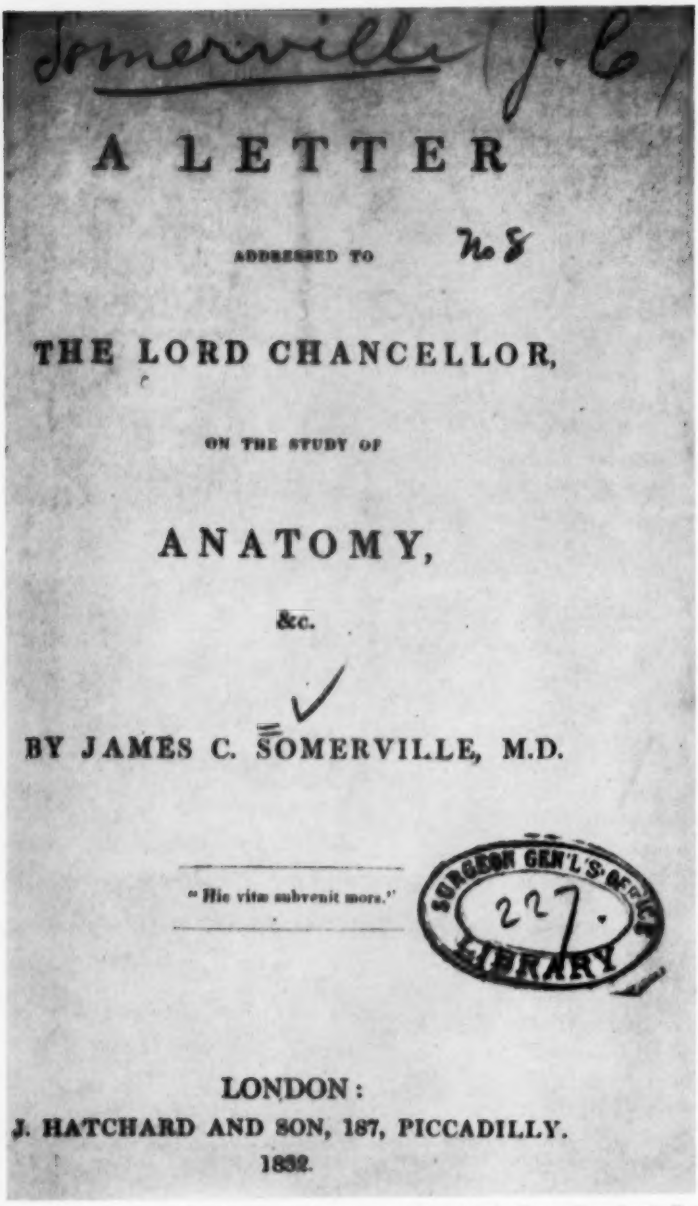
26612

BOSTON:

PERKINS & MARVIN, 114, WASHINGTON ST.

1829.

Fig. 1.—Title page to Massachusetts Medical Society's address to the community. (Reproduced with permission from the National Medical Library, Washington, D. C.)


Somerville J. C.

A LETTER

ADDRESSED TO

No 8

THE LORD CHANCELLOR,

ON THE STUDY OF

ANATOMY,

&c.

BY JAMES C. SOMERVILLE, M.D.

"Hic vitæ subvenit mors."

SURGEON GEN'L'S OFFICE 227 LIBRARY

LONDON:
J. HATCHARD AND SON, 187, PICCADILLY.
1832.

Fig. 2.—Title page to Dr. Somerville's letter to The Lord Chancellor, Lord Brougham. (Reproduced with permission from the National Medical Library, Washington, D. C.)

However, enough human bodies were not available for dissection. Relatives and friends objected strenuously to bodies of their kin being dissected; this created a formidable situation. Only bodies of murderers could be lawfully used, and these were much too few. The problem was limited to England and America for on the European mainland objection was not raised to dissection of bodies of people whose

burial was paid for by the state, provided a religious service was held.

In England and America exhumation was practiced, and in time resort was had to body snatching or grave robbing to meet the demands of professors of anatomy. Soon criminals, some of them members of organizations, were engaged in this practice. Apparently profits were satisfactory because, in New England, grave robbers were not deterred by fines of $1,000 or imprisonment for a year. Particularly in England, those who furnished cadavers occasionally resorted to murder, which, from the name of one of the most notorious murderers, came to be known as "burking." As will be mentioned again, this unwholesome state of affairs was brought to an end in England with the passage of an anatomy act. In the United States, since each state had to pass its own act, grave robbing existed through the 19th century.[13] Mall [1] said that burking was not limited to Great Britain, but also had been resorted to in Baltimore. Frey [14] and Guttmacher [15] called attention to the episode of 1886, referred to by Mall. This we believe was the only known case of burking in America.

One cannot absolve from blame a few of the professors of anatomy. Even John Hunter, according to Parsons,[12] "could manage to get the body of any person he wanted, were it that of giant, dwarf, hunchback or lord." Dr. Robert Knox,[16] the distinguished Edinburgh anatomist who, according to Garrison,[17] was the first to teach anatomy from the descriptive, histologic and comparative angles, resorted to body snatching. When he learned, however, that some bodies he had received were those of persons who had been murdered by criminals for the few pounds' profit to the murderers, he reported the murders to the crown.

The two most infamous murderers were William Burke and William Hare, of Edinburgh. Hare and his associate, Burke, admitted to 16 murders by suffocation (burking) before their crimes were detected. Burke was executed on Jan. 28, 1829; Hare, who turned state's evidence, was released on Feb. 5, 1829.[18,19] Horrible as were the Edinburgh crimes, it was a London murder, in 1831, that finally aroused Parliament.[20] On Nov. 5, 1831, two resurrectionists, Bishop and May, inquired at the dissecting room at King's College if any "material" was needed. They sold the body of a 14-year-old boy for 9 guineas. When the body was delivered, the porter communicated his suspicion of foul play to Mr. Partridge, the demonstrator in anatomy. Partridge, on superficial examination, confirmed the porter's suspicions. To delay the men so that the police could be notified, Partridge produced a 50 pound note and asked the men to wait for change. Soon afterward the police arrived and the men were taken into custody. At the postmortem examination it was proved that the boy had been murdered.

Activities of Resurrectionists in the United States

Grave robbing in New England has been reviewed in detail by Waite.[21] He could find only two colonial laws which prohibited disinterment of human bodies. These were passed in Rhode Island in 1655 and in Massachusetts in 1692. As medical preceptorships increased, the need for human bodies for dissection also increased. Waite expressed the belief that there had been considerable grave robbing in colonial New England because the number of human bodies legally available had been exceedingly limited, although the need for them had been ever increasing. Physicians and their accomplices were so skillful in their resurrection activities, however, that the public, for a long time, did not suspect any considerable amount of grave robbing.

After the American Revolution, however, when medical schools began to spring up, the public suspected that graves were being robbed, and, consequently, laws were enacted to make grave robbing illegal. Before 1818 each New England state had a law against grave robbing.

The demand for cadavers was not limited to the New England states but was made

wherever medical schools existed. Amateur resurrectionists were generally students under the leadership of the professor of anatomy or another member of the faculty. Later, because of increased demand for cadavers, the professional resurrectionist established himself to meet the demand. Most famous of the resurrectionists in Ohio was "Old Cunny," William Cunningham, who had been born in Ireland in 1807.[22] During the day he was a drayman in Cincinnati; from the year 1855 to the year of his death, 1871, he was an expert nocturnal resurrectionist. "Cunny" sold his own body to the Medical College of Ohio, and his skeleton is supposedly still in Cincinnati.

Resurrection Riots

As demands for dissection material increased, more and more graves were violated, and public resentment against medical schools mounted, both in America and in Great Britain. The discovery that a recently made grave had been robbed was broadcast to an eager public. Mobs sometimes attacked medical schools. Damage, personal injury, and even death resulted. Sometimes, also, the house of a teacher of anatomy was attacked, as was that of Dr. Knox,[16] of Edinburgh, and that of Dr. William Shippen Jr., of Philadelphia (1765). In 1788, according to Walsh,[23] the "Doctors' Riot" occurred in New York City. Much property was damaged, three or four civilians were killed, and the lives of some physicians were endangered. In Aberdeen, as reported in the *Lancet* in 1831,[24] Moir's Theatre of Anatomy was burned to the ground by a mob.

As the states adopted anatomy laws, such incidents came to an end. One of the last states to adopt a law pertaining to dissection was Ohio. In 1880, passage of the law was brought about by a bizarre occurrence. This was the finding of the body of John Scott Harrison in the building of the Medical College of Ohio on May 30, 1878.[25]

A son of William Henry Harrison, ninth president of the United States, John Scott Harrison, who had been a member of Congress for three years, died suddenly at his home in North Bend, Ohio, on May 26, 1878. He had been well liked because of his excellent character, and many persons, including a large number of residents of Cincinnati, attended his funeral on May 29. On May 30, John Harrison and George Eaton, respectively son and nephew of the deceased, came to Cincinnati to find the body of William Devin, a young friend of the Harrison family. Devin's body had been stolen from its grave and presumably was in one of the medical schools. After searching without success in the building of the Medical College of Ohio, the investigators were about to depart when they came across not Devin's body but the body of their father and uncle, John Scott Harrison! The tumult this stirred up was enormous. Benjamin Harrison, another son, later to become president of the United States, arrived in Cincinnati the following day. The newspapers added to the commotion. Although innocent, members of the faculty of the Medical College of Ohio were looked on as criminals. After a few days, excitement quieted down and the body of John Scott Harrison was deposited in the tomb of his father at North Bend, Ohio, where it seems to have been generally forgotten.

Anatomy Acts

Agitation began in England, in the 1820's, for legal sanction of dissection of human bodies and for a new appraisal of the laws as applied to the study of anatomy. The history of subsequent events is fascinating. In early numbers of the English medical weeklies, the *Lancet* and the *London Medical Gazette,* a petition on the subject from the London Medical Society to Parliament was mentioned. Also, letters and editorials were published, unfavorably criticizing methods then employed in the teaching of anatomy.[26-32] In the daily newspaper, the London *Morning Chronicle,* of Jan. 20, 1824,[33] the trial and punishment of three resurrection men were reported. The editor

commented on the harsh sentences these persons received and on the need of legal reforms. He urged that Robert Peel, the political leader, seek royal pardon for the offenders.

Regulations of the Royal College of Surgeons regarding requirements of anatomic knowledge were too rigid. Cadavers for dissection were too few to meet the demands of the increasing number of medical students and to allow the expanding need for new anatomic facts to be met. It was evident that medical students, physicians, and official bodies regulating medical licensure; legal authorities, and certain sections of the public were unhappy regarding the state of affairs and sensed the need for new legislation.

William MacKenzie,[34] a Glasgow surgeon, published a significant pamphlet in 1824. He made an appeal to the public and the government on the necessity of affording a supply of cadavers for dissection. He advocated that legal sanction be given to the use of unclaimed bodies of inmates dying in hospitals and workhouses for the study of anatomy. This, his chief proposal, anticipated the principal clause of the Anatomy Act, passed eight years later. However, MacKenzie stipulated that the granting of bodies for dissection be controlled by members of the Royal College of Physicians and the Royal College of Surgeons. Except for MacKenzie's contribution, remedial suggestions were few and unsatisfactory.

Urged by many petitions * from physicians, surgeons, professors, and students throughout Great Britain, the House of Commons, on April 22, 1828, authorized a parliamentary select committee to inquire into the matter of obtaining cadavers for schools of anatomy.[36] Parliament was fortunate in the selection of the members of this committee and especially so in the choice of its chairman, Mr. Warburton (Fig. 3). On the committee as organized

Fig. 3.—Henry Warburton. (Reproduced with permission from Ball, J. M.: The Sack-'Em-Up Men, London, Oliver & Boyd, Ltd., 1928, p. 179.)

were representative of many interests, but, since no physicians or surgeons were members of the House of Commons, a member of the medical profession was not included. After examining many witnesses, among whom were well-known surgeons, physicians, teachers of anatomy, and unnamed resurrectionists,[37] and after weighing the evidence over a period of three months, the committee made three chief recommendations in its report of July, 1828[38]: (1) sanction of the use of unclaimed bodies for the purpose of anatomic instruction; (2) condemnation of the exhumation of bodies for dissection, this evil to be prevented by the use of unclaimed subjects; (3) repeal of the law permitting dissection of executed murderers.

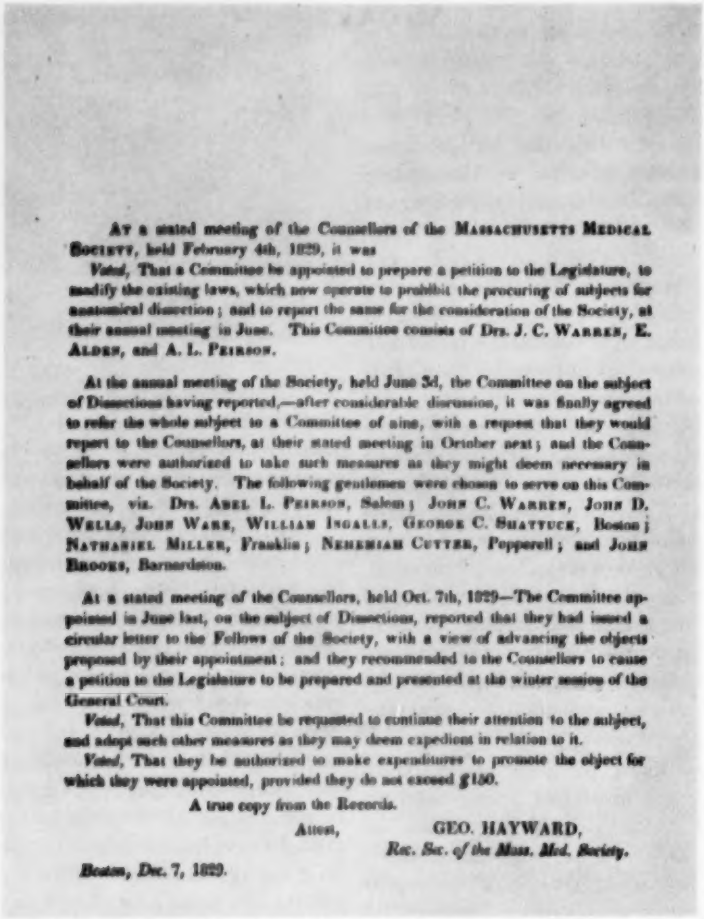
The report of the committee, and the widespread publicity given a few months later to the details of the aforementioned murders committed in Edinburgh by Burke and Hare,[18,19] hastened parliamentary legislation. Mr. Warburton introduced a disinterment and anatomy bill, in March, 1829,[39] implementing several of the propo-

* In the London *Times*,[35] between April 19 and April 23, 1828, was reported the presentation of 10 petitions respecting the study of anatomy to the House of Commons.

sals made by his committee, and it passed the House of Commons on May 19.[40] During the discussion in the House of Lords, several members, including some bishops, were opposed to the bill. Because of a rider, which granted certain powers of regulation to the College of Surgeons, the sponsors of the bill withdrew it on June 5.[41,42]

to those entrusted with the introduction of a second bill into Parliament.

At this juncture, it is well to review what occurred in Massachusetts at about the same time with regard to the problem of dissection of human bodies. A law against exhumation or concealment of a human body,



At a stated meeting of the Counsellors of the Massachusetts Medical Society, held February 4th, 1829, it was

Voted, That a Committee be appointed to prepare a petition to the Legislature, to modify the existing laws, which now operate to prohibit the procuring of subjects for anatomical dissection; and to report the same for the consideration of the Society, at their annual meeting in June. This Committee consists of Drs. J. C. Warren, E. Alden, and A. L. Peirson.

At the annual meeting of the Society, held June 3d, the Committee on the subject of Dissections having reported,—after considerable discussion, it was finally agreed to refer the whole subject to a Committee of nine, with a request that they would report to the Counsellors, at their stated meeting in October next; and the Counsellors were authorized to take such measures as they might deem necessary in behalf of the Society. The following gentlemen were chosen to serve on this Committee, viz. Drs. Abel L. Peirson, Salem; John C. Warren, John D. Wells, John Ware, William Ingalls, George C. Shattuck, Boston; Nathaniel Miller, Franklin; Nehemiah Cutter, Pepperell; and John Brooks, Barnardston.

At a stated meeting of the Counsellors, held Oct. 7th, 1829—The Committee appointed in June last, on the subject of Dissections, reported that they had issued a circular letter to the Fellows of the Society, with a view of advancing the objects proposed by their appointment; and they recommended to the Counsellors to cause a petition to the Legislature to be prepared and presented at the winter session of the General Court.

Voted, That this Committee be requested to continue their attention to the subject, and adopt such other measures as they may deem expedient in relation to it.

Voted, That they be authorized to make expenditures to promote the object for which they were appointed, provided they do not exceed $150.

A true copy from the Records.

Attest, GEO. HAYWARD,
Rec. Sec. of the Mass. Med. Society.

Boston, Dec. 7, 1829.

Fig. 4.—Minutes of the Massachusetts Medical Society regarding "Committee of Nine." (Reproduced with permission from the National Medical Library, Washington, D. C.)

Much as the reformers desired a new anatomy act, and much as those opposing it wished delay, there were clauses in the proposed legislation that would have proved contentious and difficult to administer. The experience gained in this trial of drafting legislation was subsequently of great value

with severe penalties, was passed by the commonwealth in 1815.[43] An anonymous author,† writing in the *North American Review* in January, 1831,[44] stated that in

† Dr. George Hayward, recording secretary of the Massachusetts Medical Society, is credited by many as the author.

the winter of 1829 an attempt to mitigate the severity of this law, made in the legislature of Massachusetts, was frowned on, and a bill designed to give relief did not even get a second reading. The author noted that this negative action of the legislature appeared to stimulate those who wished to legalize dissection of the human body and to give dissection a proper place in the medical curriculum. Favorable action in this direction was taken by the Council of the Massachusetts Medical Society in February, 1829, and by the society assembled at its annual session in June. The following October, the council voted to submit a petition at the next meeting of the legislature. The excellent matter and arrangement of the petition, as well as the methods used in presenting it to the public as an address to the community, produced favorable effects [9] (Figs. 1, 4, and 5). During the session of the legislature of 1830, the judiciary committee reported a great change in public opinion regarding study of human anatomy, and the governor of the commonwealth, in June, in his message to the legislature stressed the importance of the problems.[45] The Massachusetts Medical Society, in its meeting of the same month, commended the governor for his support and gave the council of the society full powers to act in any way it thought proper in order to accomplish the desired legislative action. At the next session of the legislature, in 1831, an anatomy bill was submitted and became law.[46] The content of the main clauses was substantially as follows: 1. Severe penalties were prescribed for exhumation of a body. 2. Certain public officials lawfully could surrender to qualified physicians the bodies of unclaimed dead, for anatomic instructions. 3. Any licensed physician or medical student lawfully could use human bodies for anatomic inquiry. In the *London Medical Gazette* of Jan. 21, 1832,[47] passage of this Massachusetts anatomy bill was reported, thus adding record of this accomplished fact to its many arguments in favor of a similar measure being placed on the books of Great Britain.

Fig. 5.—George Hayward, recording secretary of the Massachusetts Medical Society. (Reproduced with permission from the Harvard Medical School.)

Now to return to the British Isles: From June, 1829, to December, 1831, the problem of new legislation to regulate the study of anatomy was the subject of lively discussion before medical societies,[48] of contention between editorial offices of medical and lay journals,[49] and of numerous petitions to the houses of Parliament. Mr. Warburton was commended by his constituents at Bridport [50] for his previous endeavors and was urged to renew his efforts. The teachers of anatomy were divided as to the merits of the old system of procuring bodies and a possible new method.[51] A group of teachers of anatomy in Dublin advocated, and solicited, volunteers to will their bodies for anatomic study.[52] The surgeon, Mr. Guthrie, in a letter to Lord Althorp,[53] and at a lecture to the Royal College of Surgeons in London,[54] unfavorably criticized the previous anatomy bill and maintained that enough consideration had not been given to the

Fig. 6.—Thomas Wakley. (Reproduced with permission from Sprigge, S. S.: The Life and Times of Thomas Wakley, New York, Longmans, Green & Co., Inc., 1897; opposite page 328.)

advice and suggestions of the College of Surgeons.

Mr. Thomas Wakley[55] (Fig. 6), surgeon and editor of the *Lancet*, took issue with Mr. Guthrie and advocated regulation by a commission, the majority of its members to be laymen. A clause constituting such a body had been included in the first anatomy bill. The editor of the *London Medical Gazette*[56] wished a new bill but evidently disagreed with Mr. Wakley in many details. Thus began a journalistic controversy which persisted for many years and, in minor degree, reflected opposing political views of the times. Mr. Wakley was the reformer, Liberal or Whig; in contrast, the editor of the *London Medical Gazette*, Dr. Roderick Macleod, was the Conservative, or Tory. Wakley advocated severe penalties for exhumation and sale of human bodies and opposed the proposal that the College of Surgeons have regulatory authority over the schools of anatomy. Macleod recommended that dissection of executed murderers be allowed and that the College of Surgeons have regulatory authority. The three strongholds of the Conservatives were the College of Surgeons, College of Physicians, and Society of Apothecaries.[57] These organizations naturally defended their charters and legal rights, while a considerable body of the medical profession desired a new approach to pressing problems, including wider application of human dissection in the study of anatomy. Mr. Wakley was an active medical and social reformer and took the lead for the forward-looking group.[58,59]

The desire for reform was general and in the political air of the time. The famous reform bill, introduced by liberal statesmen, in order to eliminate the so-called rotten boroughs, to increase the number of urban and county constituencies, and to broaden the suffrage of voters, was at the time under debate in Parliament and became law in June, 1832. The act abolishing slavery in the British colonies was passed in the next year, August, 1833.

Mr. Warburton, on Dec. 15, 1831, introduced a second anatomy bill in the House of Commons and stated that the new bill would be shorter and simpler than the first.[60-62] This was the initial step in a determined effort to set up workable legislation.[63,64] While the bill was in committee an amendment was passed, which replaced the words "lawful custodian" by the expression, "any executor or other party having lawful possession" of an unclaimed body.[65] The alteration reflected an appreciation of the laymen's sensitiveness to possible police action by the person vested with this responsibility.

At this stage, two important letters were addressed to members of the government, Lord Melbourne,[66] minister of the Home Department, and Lord Brougham, Lord Chancellor.[67] The first was from the Coun-

cil of the College of Surgeons, in which numerous faults in the system of studying anatomy were admitted and their own college regulations were censured for forcing the student to dissect the human body and thus to commit an illegal act. However, no specific remedies were suggested. This communication was published in the *Lancet* and in daily newspapers. The second letter, written by Dr. James Somerville[67] and addressed to Lord Brougham, had a legal flavor; it contained a complete summary of the difficulties involved and suggested solutions of the problem (Fig. 2). It is only fair to state that Benjamin Brodie,[68] the eminent surgeon and a member of the Council of the College of Surgeons, early in 1832 advocated remedies similar to those suggested by Dr. Somerville. Another advocate of Somerville's suggestion was Dr. Robert Ferguson.[68] Several of the proposed remedies were incorporated in the bill then before the House of Commons. In letters to the medical journals and petitions to Parliament,[69] unfavorable criticism or support of the measure, continued to be offered. An intelligent petition from the citizens of the City of Leeds[70] supported the main objectives of the bill.

The next significant event was a speech made by Thomas Babington Macaulay (Fig. 7), afterward Lord Macaulay, in the House of Commons on Feb. 27, 1832.[71,72] Macaulay replied to an attack made on the bill by Mr. Hunt, an energetic opponent, whose main criticism was that the present bill was for the benefit of the rich, at the expense of the poor. Macaulay's speech was a brief but masterly statement of the chief reasons why he and others favored the bill. He stated that there were two main evils, which the bill attempted to remedy: First, the practice of burking and second, bad surgery. The poor would suffer most, he claimed, if the bill failed to become law. He also emphasized that the improvement in surgery resulting from accurate knowledge of human anatomy was not a mere question of science. "It was a question between health and sickness, between ease and torment, between life and death."

Fig. 7.—Thomas Babington Macaulay. (Reproduced with permission of the University of Minnesota Library from a painting by S. W. Reynolds Jr. Taken from the *Eclectic Magazine of Foreign Literature, Science and Art*, Vol. 1, January, 1844, Frontispiece.

Macaulay then related that the horse of Leopold, Duke of Austria, who lived in the 12th century, fell and crushed the Duke's leg. Surgeons advised amputation but knew of no satisfactory method. Leopold ordered his servant to cut off the leg. A gush of blood resulted and the duke died. Now to quote Macaulay: "There is not now a bricklayer who falls from a ladder in England, who cannot obtain surgical assistance infinitely superior to that which the sovereign of Austria could command in the twelfth century."

Macaulay closed his speech by stating, "I think this bill tends to the good of the people, which tends especially to the good of the poor; therefore, I support it."

Discussion of the anatomy bill continued in the House of Commons for several weeks. Sponsors, both within and outside of Parliament, became impatient with the delaying

Important Events That Led to Passage of the Anatomy Acts

Year	Month	In Great Britain	In Massachusetts
1815	March		Act passed to protect sepulchers of the dead
1828	April	Parliamentary committee of inquiry authorized	
	July	Report of parliamentary committee	
1829	March	Anatomy bill introduced in House of Commons	
	May	Anatomy bill passed by House of Commons	
	June	Anatomy bill withdrawn from House of Lords	
	December		Address to the community by Massachusetts Medical Society regarding study of anatomy
1830	June		Report of committee of House of Representatives
1831	March		Anatomy bill became the anatomy act
	December	Second anatomy bill introduced in House of Commons	
1832	January	A letter of Dr. Somerville addressed to the lord chancellor	
	May	Second anatomy bill passed by House of Commons	
	July	Second anatomy bill passed by House of Lords	
	August	Second anatomy bill became the anatomy act	
1834	April		Certain amendments to anatomy act of 1831

tactics of the opposition.[73] The bill passed the House of Commons on May 11.[74] It was introduced on May 20 in the House of Lords and was passed by that body on July 19.[75,76] "An Act for Regulating Schools of Anatomy" became effective on Aug. 1, 1832[77] (Table).

The important clauses of the act, which the secretary of state for the Home Department was authorized to administer, had the following provisions: 1. It would be lawful for any executor or other party having lawful possession of the body of any deceased person to permit anatomic examination of the body. Safeguards were emphasized to protect the wishes of the deceased subject or those of close relatives. 2. Licenses were to be granted to certain specific persons to practice anatomy. 3. Inspectors of anatomy would be appointed and would supervise the lawful supply and distribution of bodies to the schools. 4. Persons possessing human bodies for anatomic study were not liable to legal prosecution. 5. Bodies of executed murderers were not to be dissected.

Editorial comment on the act indicated that the majority of its sponsors expected it to be effective and were anxious to give the administrators of the new law a fair trial. Mr. Wakley, editor of the *Lancet*, however, remained unfavorably critical of the legislation because of the absence of penalties for buying and selling human bodies.[76] He predicted that burking would not cease.[64]

Administration of the British Anatomy Law, 1832 to 1842, and New Legislation in the United States

The government realized the importance of the part that an inspector of anatomy would play in enforcement of the new law. To be successful he would have to possess a thorough grasp of the intent of the law, personal initiative, and a cooperative spirit. The Home Office, after deliberation, appointed James Somerville, M.D., inspector of anatomy for metropolitan London and the English provinces. Dr. Somerville[67] has been mentioned before in this article. The choice proved to be a wise one. The new inspector soon devised ways for an applicant to obtain a license to practice dissection, and he organized a system of records, which included confidential returns from the schools of anatomy.[78] For the first few months there were complaints from students and teachers of anatomy regarding administration of the law,[79,80] but during the remainder of the year the new system functioned satisfactorily.[81,82]

Unfavorable criticism was made during the second session, 1833 to 1834, especially with regard to the supply and distribution of bodies for dissection. Letters and editorials, for and against the methods of administration, were published in medical journals and newspapers. Former severe critics were active again[83-87]: the Council of the College of Surgeons,[88] certain teachers of anatomy, and the editor of the *London Medical Gazette*.[89,90] In January, 1835,

a commission of inquiry of the College of Surgeons, in contrast to their previous unfavorable criticisms, made a favorable report to the Home Office on the accomplishments of the inspector and asserted that the chief difficulties arose from decrease in the general death rate and jealousy among teachers of anatomy.[91,92] At this time, the result of an inventory of bodies for dissection in four of the larger London schools was satisfactory to all concerned.[90] Favorable reports on the working of the anatomy act were published by teachers of anatomy in Dublin,[93] Belfast,[94] and Glasgow [95] in the years 1835 to 1839. In Edinburgh,[96] difficulties arose in the first years of application of the act, but with the resignation of the first inspector of anatomy there, the administration improved greatly.[97] In the succeeding years, the actual cost of dissection to the student in Edinburgh was reduced from 5 to 3 pounds.[98]

In the sessions of 1839 to 1840 and 1840 to 1841, a reduced number of deaths in London led to a dearth of bodies for the schools of anatomy. Unfavorable criticism of the administration was similar to that in 1834.[99,100] However, as in 1835, improvement was satisfactory and, before the end of the school year of 1841, unfavorable criticism of the inspector, Dr. Somerville, was replaced by praise.[101]

The anatomy act was administered, as a rule, with minimal publicity. In 1840 two items of news relating to its administration, in districts distant from London, were reported in the *Lancet*. Certain students attending the South Infirmary in Cork, Ireland, were prosecuted and held for trial on the charge of illegally practicing anatomy.[102] The second incident took place in Newcastle upon Tyne, in December of the same year.[103] Under instruction of the parish officer, the janitor of the Newcastle School of Medicine and Surgery removed a body, thought to be unclaimed by relatives, from the subject's abode to the medical school. When a complaint was made to the mayor of the city by a supposed relative, the mayor ordered the body to be removed from the school and buried in the usual manner. An official inquiry was made a few days later, and the magistrate ruled that even though the medical school and the civil authorities had acted legally, the public sensitiveness in such matters demanded an interpretation of the law in favor of the supposed relative. The attitude of the magistrate in Newcastle was in harmony with the spirit of the anatomy act as advocated by the original legislators.‡

During the next two years attempts were made to amend the act. In October, 1841, Mr. Morrison, a surgeon, suggested to the meeting of the North of England Medical Association that the association petition Parliament to make specific alterations in the act, so that it would be compulsory for the executor of an unclaimed body to deliver it when it was demanded by a teacher of anatomy.[104] This suggestion was reminiscent of a similar, and unsuccessful, proposal made by the College of Surgeons 10 years before. Questions were asked repeatedly in Parliament regarding the working of the act.[105] The government preferred to make any necessary changes in enforcement by means of departmental regulation rather than by new legislation.[106,107] Quiet regulation was favored by the majority of the members of Parliament, the public, and the medical profession. In contrast, in the Commonwealth of Massachusetts changes in the administration of its anatomy act of 1831 were accomplished by new legislation enacted in 1834 [108] (Table).

After a decade of varying fortune, the anatomy act of England was firmly established. In October, 1842, Dr. Somerville resigned from the inspectorship,[109] and the secretary of state for the Home Office filled

‡ One of us (N. M. K.) was a pupil of Prof. J. Playfair McMurrich, Department of Anatomy, University of Toronto, in 1907. Discussing his personal reaction to the procurement of bodies for dissection in the Province of Ontario, he stated that it was a continual subject of personal worry to him, because reports of mistakes were likely to reach and disturb the public.

the vacancy by appointment of two inspectors for England, one for the metropolitan district of London and one for the provinces.

Comment

Many medical and social problems of the 1820's and 1830's were solved by the good sense of the British and New England peoples. We have sketched the agitation and the methods brought forward to remedy a serious medical anomaly.[110,111] Legislative action on both sides of the Atlantic led to satisfactory laws, which have stood the test of time for more than a century. In Massachusetts, the unity of action of the medical profession, over a relatively short period, is in striking contrast to the prolonged and devious activities of organized medicine in England. Perhaps the small population of Massachusetts, one-fortieth of that of Great Britain, and the fact that the commonwealth was young made the attainment of unified action easier in Massachusetts than in Britain. In both lands the fundamental new suggestion, of using the bodies of unclaimed dead for purposes of dissection, abolished both the trade and the crimes of the resurrectionists, as well as the illegal procedures of medical students and practitioners. In England, at least, of the two fundamental psychologic hurdles, that (1) of ignorance and prejudice of the public, proved less formidable than that (2) of clash of interests of medical institutions. The rumblings of self-interest, from the colleges of surgeons and physicians, from the Society of Apothecaries, from the long-established hospitals, and from the schools of anatomy, took time to subside.

The legislative committee of inquiry, in this instance the select anatomy committee of the House of Commons, appointed in April, 1828, and sitting for the next three months, performed a great service to the nation. Its thorough report contained the basic concepts of subsequent successful legislation. Members of this committee included Henry Warburton, Joseph Hume, Poullet Thomson, and Robert Peel. Warburton, Hume, and Thomson were members of the liberal reform party, while Peel was the rising leader of the enlightened Tories.

It is worth while to recall that considerable time is required to pilot new legislation through the various stages of parliamentary procedure. Perusal of the parliamentary news regarding the anatomy bills in the *Times*, *Chronicle*, and *Morning Post* reveals how persistent and patient their sponsors were for months. Also, reading such as has been mentioned reveals the give and take of debate, the acceptance or rejection of a clause or phrase, while the bills were passing through the committee stage. Mr. Warburton appeared to have the requisite grasp of the main objectives of the bills and the necessary support when the House divided and votes were counted. He stressed the permissive, in contrast to the compulsive, surrender of unclaimed bodies by the constituted civil authority to the schools of anatomy. On the day of passage of the second anatomy bill, May 11, 1832, by the House of Commons, the confidence of its sponsors was evident, and Mr. Warburton closed the final debate by stating that all the facts of the bill had been discussed many times and there seemed no need of repeating them; surely the house would react favorably, he said. As we noted previously, Thomas Babington Macaulay, the young reformer, lawyer, and man of letters, did yeoman service in the house in support of the bill. Subsequently, Macaulay became the ablest committeeman of his time and was chosen chairman in 1847 of the select committee to study Wakley's suggested medical reform bill.[112] Trevelyan,[113] Macaulay's biographer, in recording the stirring events of the 1830's, stressed that the times had developed a type of politician whose personal reputation, whether literary, political, or forensic, held its own against the advantages of birth, rank, and wealth. Surely Macaulay, Warburton, Hume, Thomson, and Peel were parliamentarians of this type, and gratitude both of the medical profession

and of the public is due to these laymen, among many others, who recognized clearly the importance of the study of anatomy to the people of Great Britain and possessed the vision and competence to sponsor successfully the needed reforms. These British legislators were politically courageous in supporting the new law, not only during debate in parliament, but on the hustings during popular elections.[114] The governor and other legislators in Massachusetts, in 1830 and 1831, in a similar fashion gave their support to a reformed anatomy act.

Certain members of the medical profession deserve great credit for the parts they played in bringing about needed reforms in the anatomy laws. The committee of nine of the Massachusetts Medical Society, and George Hayward (Fig. 5), the secretary of the society, realized the importance of boldly placing the problem before an antagonistic public and legislature in 1829. Their frank policy succeeded sooner, and to a greater degree, than they anticipated. In Great Britain three reformers, James Somerville, Thomas Wakley, and Professor Jones Quain, men possessing outstanding gifts in different fields of medical endeavor, supported the anatomy reforms from the period of agitation through the struggles in the legislature and the first decade of enforcement of the new law. Somerville was a young teacher of anatomy who possessed a thorough grasp of the requirements of students. He also succeeded in creating a spirit of mutual respect between the administrators of the law in the parishes and those in the Home Office of the government. Somerville's ability and patience gradually overcame the opposition of the conservative surgeons and professors of anatomy.

From the inception of the *Lancet*, in 1823, Wakley's editorial pen advocated numerous medical reforms,[112] including the anatomy laws. He was particularly forceful in revealing the monopolistic power of the Council of the Royal College of Surgeons over the medical curriculum and over licensure of English practitioners. Ceaselessly he attacked the status quo. Many libel actions resulted from his vigorous advocacy of a new deal in medicine, and yet his persistent activity for medical reforms led to his election to a seat in the House of Commons, in 1835, and the coronership of West Middlesex, in 1839. He was the first medical practitioner to occupy the office of coroner in England. Wakley unfavorably criticized the anatomy act because it did not specifically enumerate severe penalties for those who traded in bodies for dissection. He, like the members of the legislature of Massachusetts, believed that if such penalties were not imposed, body snatching would continue indefinitely. However, after passage of the anatomy acts, the trade of the resurrectionist gradually ceased. Even the earnest, enlightened reformer is not always an accurate prophet.

Jones Quain was a great anatomist and professor of anatomy in the University of London. He strongly endorsed the recommendations of the special anatomy committee of the House of Commons and became one of a small group of anatomists in London who enthusiastically encouraged the governmental authorities,[84,87] as they put the new law into practice. His article, "Obstructions to the Science of Anatomy," published in the *Monthly Review* in January, 1832,[11] is a lucid, complete summation of the reasons for reform of the existing anatomy laws.

A glance backward over a short period of history is enlightening. We have recorded details of a medical social problem which arose in the first half of the 19th century. When possible solutions were discussed, divided counsel prevailed in the medical fraternity; the public, therefore, was suspicious of suggestions made by medical organizations. Both parties pressed for a just solution. In Britain, among others, a patient, gifted liberal, Warburton, led the political laymen, and a fighting medical reformer, Wakley, represented the medical profession. Slowly but surely compromise legislation was devised which proved wise and helpful

to both parties and to the people generally. Enactment of the anatomy laws was a good example of medical and political wisdom equitably shared.

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Esophageal Ulcer in the Adult

Clinical Aspects and Experiences with Conservative Treatment

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Esophageal ulcer has a well-deserved reputation for seriousness due to the constant threat of hemorrhage and perforation.[1] In fact, because of these dangers a radical surgical approach to therapy may be indicated in a portion of cases and has been urged by some clinicians as proper for most cases.[2] One notices, however, that recently reported series[3,4] of esophageal ulcer patients show a considerably smaller proportion of serious complications than many of the older series.[5,6] It is highly unlikely that there has been any change in the behavior of the lesion; rather, it appears that formerly a good many esophageal ulcers made their presence known only through their complications, while more recently the increasing popularity of medical esophagoscopy has served to bring to light many ulcers which otherwise would have gone unrecognized.

Primary esophageal ulcer usually occurs as a single lesion and almost always involves the distal one-third of the organ. It is ordinarily considered a "peptic" ulcer, akin in an undefined way to duodenal ulcer and gastric ulcer. There are general histopathologic similarities, and, in addition, the patient with an esophageal ulcer often has an ulcer of the stomach or duodenum. "Primary" as applied to this lesion indicates that no corrosive agent, foreign body, tumor, specific infectious agent, or extrinsic pressure is active in etiology and that the ulcer is not associated with uremia, skin burns (Curling ulcer), or brain injury (Cushing ulcer). It does not exclude ulcers which are associated with hiatus hernia. Many aspects of clinical course and management are different in adults than they are in infants and young children.

This report summarizes clinical observations made among a group of adults with primary esophageal ulcer who were treated by conservative medical means.

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Patient Group

Twenty-three patients with primary esophageal ulcer were studied and observed for varying periods during and following treatment. They were selected by the single criterion that therapy was conservative. Seven were women and two were Negroes, the others being Caucasian men. The ages ranged from 22 to 85 years, the number of patients per age decade from the third through the ninth decades being, respectively, 2, 4, 4, 5, 5, 2, and 1. The periods of observation varied from three months to eight years: three months, two patients; four months, three; six months, four; one year, two; two years, one; three years, eight; four years, one; four and one-half years, one, and eight years, one.

TABLE 1.—*Associated Diseases, Either Present at the Time the Esophageal Ulcer was First Detected or Developing Later in the Course*

Ulcers	
Of duodenal bulb	4
Postbulbar	1
Gastric	2
Anastomotic	1
Hiatus hernia	6
Diffuse mucosal disease	
Esophagitis	9
Esophageal leukoplakia	2
Erosive gastritis	1
Carcinoma	
Proximal esophagus	1
Stomach	1
Other esophageal diseases	
Diverticulum	2
Varices	1
Others	
Diverticulosis coli	1
Chronic cholecystitis	1
Hyperthyroidism	1
Arterial hypertension	1
Portal cirrhosis	1

Sixteen of the patients had one or more associated diseases which might have had some symptomatic, etiologic, or common causal relationship with esophageal ulcer (Table 1). Six patients had one ulcer elsewhere, and a seventh had a gastric and a duodenal ulcer in addition to the esophageal ulcer. There was a direct hiatus hernia in six patients and erosive esophagitis in nine. It may be that the former has some etiologic importance and the latter some common etiologic basis. In connection with the widely accepted but by no means proved theory that there is an acid-peptic basis for esophageal ulcer, it is of interest that the ulcer in one patient developed three months after vagotomy and gastroenterostomy.

Subjective Pictures and Complications

In view of the large number of associated diseases, it was difficult in many cases to separate from the total symptom patterns those complaints which could properly be attributed to the esophageal ulcer. This was, of course, especially true of patients with gastric or duodenal ulcer or hiatus hernia. Difficulty was encountered, too, in attempting to judge the apparent duration of the esophageal ulcer from the duration of the symptoms and from changes in the individual symptom patterns. Thus, in one patient who had had symptoms for only two weeks an obviously chronic esophageal ulcer with moderate stricture was found. Another patient, who had been observed periodically for three years because of an uncomplicated hiatus hernia, was suddenly discovered to have developed an esophageal ulcer, although his symptoms meanwhile had not changed. On the other hand, in about half the cases it was found that the symptoms served as a particularly accurate barometer of the organic changes, a phenomenon which is often observed in nonulcerous esophageal diseases.

TABLE 2.—*Presenting Complaints, Symptomatic Features, and Subjective Role of the Complications*

Most important presenting complaint attributed to esophageal ulcer	
Hematemesis	2
Obstructed swallowing	8
Subxiphoid pain	13
Total symptomatic features, early and late, attributed to esophageal ulcer	
Bleeding	5
Weight loss	12
Pain during swallowing	10
Pyrosis and pain following meals	3
Obstructed swallowing	12
Nocturnal subxiphoid pain	3
Complications contributing symptoms	
Bleeding	5
Stricture	7

The subjective features are shown in Table 2. It is necessary to consider the complications when evaluating specific symptom patterns because of the important part played by them in about half the cases. Two patients had severe hemorrhages from the ulcer, and, although they had previously had some pain on swallowing, it was the bleeding which first caused both to seek medical help. Three others bled later in their courses. Similarly, there was the complaint of obstructed swallowing in each of the seven patients who had developed secondary esophageal stricture, although this was also a problem in five other patients who did not form a stricture.

The single commonest complaint attributable to esophageal ulcer was pain, felt deep beneath the distal gladiolus or xiphoid. In a few patients there was radiation to the midback, to the left neck and shoulder region, or to the left nipple area. In 10 patients the pain was aggravated during meals. This was not necessarily true odynophagia, for often the bolus went down painlessly and it was only several seconds later that the pain appeared. In three cases there was no pain during meals, but approximately a quarter hour later pyrosis with rather severe pain began. Weight loss, a common complaint, appeared to be attributable to the fear of painful meals rather than to obstructed swallowing. Nocturnal pain was a problem for three patients.

Diagnosis and Pathology

In line with common experience, it was found that esophagoscopic examination was by far the most effective means of establishing the diagnosis. In 20 cases the lesion was easily studied endoscopically and recognized as a benign ulcer. In the three others, the degree of secondary stricture was such that it was not possible to reach the roentgen-demonstrated lesion with the esophagoscope,

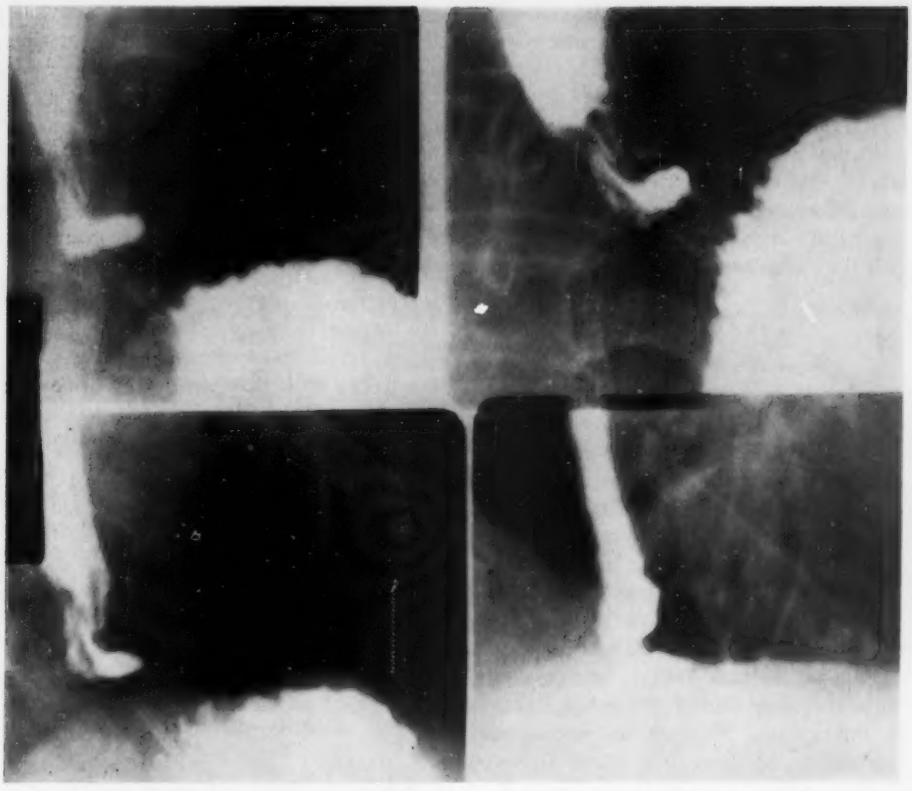

Fig. 1.—Clear-cut roentgenologic evidence of an ulcer crater, such as this, is unusual.

and no ulcer was seen. On the other hand, an actual crater could be demonstrated roentgenologically in only seven instances (Fig. 1). In nine the radiologist believed there were indirect signs of esophageal ulcer, and in the other seven he did not suspect the diagnosis.

Only one esophageal ulcer was found per patient. All lay within the distal 5 cm. of the esophagus: one was 5 cm. above the esophagogastric mucosal junction; two were 3 cm.; six, 2 cm.; six, 1 cm., and eight were astride the junction. Nine of the ulcers involved mainly the right lateral aspect of the esophageal circumference; eight lay on the left; five, on the posterior wall, and one surrounded the esophagus as a girdle ulcer. Seven of the lesions were judged to be circular, fifteen were oval, and the last was, of course, band-like. The maximum estimated or transesophagoscopically measured diameter of the lesions at the time of diagnosis was 4 mm. in one instance, 5 mm. in seven, 6 mm. in one, 7 mm. in one, 8 mm. in four, 10 mm. in three, 13 mm. in one, 15 mm. in four, and the whole circumference of the esophagus in one.

The lesions had a characteristic unevenness to their bases and were deeper at their distal edges than at their proximal. These features could be observed only endoscopically and only after the craters had been swabbed clean. In two instances there were polypoid epithelial excrescences along the proximal edge of the crater.

One or more biopsy specimens were taken of the ulcer edge in 19 cases. The common histopathologic finding, as revealed in 15 instances, was chronic subepithelial and submucosal inflammatory infiltration and

fibrosis. In all but four cases the epithelium was normal to the edge of the crater itself. There was a zone of acute inflammatory infiltration of the epithelial layer about the crater in one case, and moderate periulcerous epithelial hyperplasia was found in three others. The biopsy specimen contained only amorphous necrotic material and acute inflammatory exudate in two instances and only normal mucosa in two others.

Treatment

Treatment of all patients was based upon oral bismuth subcarbonate and periodic esophageal dilatations. In addition, all but one of the patients with gastric or duodenal ulcer were treated by prolonged interview therapy, and the patient with arterial hypertension received sedation from time to time. The patient with gastric carcinoma was managed by palliative gastrojejunostomy while under treatment for the esophageal ulcer, and portacaval shunt was carried out for the patient with cirrhosis and esophageal varices. Hiatus hernia repair was not done in this group. No antacids per se, antispasmotics, or diets were used, nor were tobacco, coffee, or alcohol interdicted.

Bismuth subcarbonate was given in 2 gm. doses, made into a heavy paste with water and taken one-half hour after each meal and at bedtime. It was prescribed over a period which averaged about three months. Bismuth subcarbonate is an efficient astringent and probably for that reason proves remarkably effective in the treatment of esophageal erosions and ulcers.

For patients who had developed no stricture, esophageal dilatations were carried out on an average of about twice per week during the first month of treatment. Dilatation was done daily, as long as the individual problem demanded, for those patients whose ulcer was complicated by stricture. In both situations Hurst mercury bougies were used, and the plan was to progress to and continue with a No. 48 F. The usefulness of dilatations in uncomplicated esophageal ulcer is a bit difficult to explain. That they provide considerable symptomatic relief is obvious; that they encourage ulcer healing is probable, as best one can judge from objective evaluation. There is the effect of temporarily breaking up segmental spasm, but there must be more to the explanation than this. There appears to be no danger of initiating hemorrhage or any other complication through dilatation, and it offers good prophylaxis for the time being against stricturing.

The role of psychogenic influences in the etiology of esophageal ulcer is not understood. One's impression is that they are of much less importance than they are in the case of duodenal ulcer; nevertheless, when esophageal ulcer is associated with duodenal ulcer, both lesions tend to heal and to become reactivated simultaneously. In the present series interview therapy was used to supplement esophageal ulcer management quite by happenstance, but it is important to understand that interview therapy helps any patient, whether he is sick from functional disease or carcinomatosis.

Results—Clinical Course

At the completion of the courses of observation, it was concluded that the subjective results of treatment had been excellent in nine cases, fairly good in nine, and poor in five. This was judged on the basis of the permanency of relief of such symptoms as dysphagia, pain, and weight loss. Permanency is emphasized rather than mere relief because all patients were helped considerably during active treatment. Esophageal ulcers do not show the same tendency to recur that duodenal ulcers do, but recurrence of symptoms following healing is common, presumably because of segmental motility abnormalities about the irritant focus.[7] The nine patients who responded excellently to treatment lost their symptoms quickly and had no recurrence during their period of observation. The nine whose response was judged to be fairly good had pain or dysphagia from time to time for a few weeks following ulcer healing and none thereafter. The five who responded poorly

continued to have recurrences of symptoms, believed properly to be ascribable to ulcer, following its healing.

It seems particularly significant that three of the five patients who responded poorly showed electrocardiographic evidence of pericarditis, without other signs of heart disease, as treatment progressed. The first case was recognized quite by chance through routine electrocardiographic study. Although thereafter one or more tracings have been made in all cases of ulcerative esophageal disease, a total of only 10 of the present series came under this program. Nevertheless, the only three patients who evidenced any significant abnormality—pericarditis in all three—were those who had persisting symptoms. In the absence of anatomic knowledge of the conditions which existed between the area of ulceration and the nearby pericardium, it is difficult to render an interpretation. Presumably periulcerous fibrosis, possibly aggravated by local penetration, had reached the pericardium, with a certain degree of inflammatory irritation.[8]

Fig. 2.—This huge crater, which measured 15 mm. in diameter at its edges but was much larger in its depths, lies astride the esophagogastric mucosal junction. It healed completely within eight weeks. (Note that this lesion is remarkably similar to that pictured by Allison[8] in his Plate XV(*a*))

TABLE 3.—*Status of Ulcer upon Successive Repeat Esophagoscopic Examinations During Treatment and Later Observation—Twenty-One Patients*

Interval Since Previous Examination	Status of Ulcer		
	Not better	Better	Healed
2 wk.	2		2
4 wk.	2	6	11
6 wk.		1	9
8 wk.		1	2
9-12 wk.	2		
20-25 wk.			2
3 yr.			2

Objective evaluation of the progress of an esophageal ulcer requires both esophagoscopic and roentgenologic study, the first because it is most effective for investigation of healing of the ulcer itself and the second because it best permits detection of secondary stricturing. Even though esophageal ulcers have little tendency to recur, they tend to create a chronic problem by stricturing upon healing. All of the patients had radiologic study at or toward the end of their observation period, and 21 had at least one repeat esophagoscopic examination at the completion of study. A total of 42 repeat esophagoscopic examinations was made after treatment had been begun.

By both endoscopic and radiologic criteria the objective results of treatment were good in all patients (Fig. 2). The ulcers all healed, requiring periods which varied from two weeks to three months and averaged about four weeks. These are approximate figures because esophagoscopic examinations were not made at close intervals, the exact time of ulcer epithelialization could not, of course, be determined. The findings on successive esophagoscopic studies are shown in Table 3. New strictures did not develop during the period of observation.

Three patients died during the study, and all were examined by necropsy. One patient died of neglected perforation of a gastric ulcer, which occurred while he was on a camping trip. Autopsy showed that his esophageal ulcer had not become reactivated simultaneously with the gastric ulcer. The esophageal mucosa was intact, although there was considerable intramural fibrosis. The two patients with carcinoma eventually died,

and at autopsy their ulcers were found to be well healed.

Summary and Conclusions

Twenty-three patients with primary esophageal ulcer, selected because they were treated by conservative medical measures, are reported. The frequency of associated diseases, especially gastroduodenal ulcer, hiatus hernia, and subacute erosive esophagitis, was notable. The main symptoms believed ascribable to esophageal ulcer were weight loss, painful swallowing, obstructed swallowing, and bleeding. Diagnosis by esophagoscopic examination was considerably more efficient than by roentgenologic study. Treatment consisted of oral bismuth subcarbonate, periodic esophageal dilatations, and, in some cases, interview therapy. All of the ulcers were followed to proved healing, and this required a period which averaged about four weeks. Nine patients lost their symptoms quickly and had no recurrence. Nine had recurrent symptoms for a few weeks following ulcer healing, and five continued to have recurrent symptoms, believed ascribable to persisting esophageal motility disturbances, following ulcer healing. Three of the latter five had electrocardiographic signs of pericarditis. The objective results of treatment were good in all cases. No strictures developed.

Conservative management is not being recommended as a routine approach to every primary esophageal ulcer. The danger of complications, particularly severe hemorrhage and perforation, are emphasized although not dealt with specifically in this presentation. Complications are a consequence of therapeutic neglect, and it is demonstrated that, when an esophageal ulcer is diagnosed prior to any major complication other than hemorrhage, simple but vigorously applied medical treatment produces safe and satisfactory results. The main late complication of healing, stricture formation, can be prevented if dilatations are made part of treatment.

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Bacterial Shock

A Clinical Analysis of Thirty-Eight Cases

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The physiological disturbances produced by the blood-stream invasion of bacteria or their products manifested by peripheral vascular collapse has been called bacterial shock. This entity, although it occurs not infrequently and has also been produced in the experimental animal, is poorly understood.[1-5]

The experimental syndrome has been produced by the intravenous injection of an endotoxin obtained from certain Gram-negative organisms.[1-5] Thomas [2] describes this endotoxin as a group of toxic substances which exist as a phosphorus-containing, polysaccharide, protein-lipid complex. The polysaccharide contributes immunological specificity; the protein is closely bound to the polysaccharide and when separated is toxic if in combination with the phosphorus-containing radical. This latter radical also seems to confer toxicity on the otherwise nontoxic polysaccharide.

The physiological changes which occur following the intravenous administration of this endotoxin in animals have been reported by several authors [2-7] and include profound vasomotor collapse, characterized by alternating arteriolar constriction and dilatation, followed by prolonged dilatation; high fever, occasionally followed by hypothermia; marked leukopenia, followed by leukocytosis; hyperglycemia, followed by hypoglycemia; depletion of liver glycogen and accumulation of lactic acid in the blood and tissues, with a resulting metabolic acidosis, and hemorrhagic necrosis in rapidly growing tumors.

The occurrence of shock following Gram-negative bacteremias is relatively common,[1,8-11,13] while peripheral vascular collapse with Gram-positive bacteremias is less common.[4,11,12] Although a large number of Gram-negative organisms have been shown to contain endotoxin, notably Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris, Salmonella typhosa, Shigella, and the meningococcus, there is no available evidence that endotoxin exists in Gram-positive organisms.[14] The mechanism of shock in the latter instance may be due to a true bacterial hypersensitivity reaction and not to endotoxins. Stetson [6] has shown that bacterial sensitivities can be induced in animals and that subsequent reactions to the offending bacteria closely simulate reactions to endotoxin. Although the mechanism of shock produced by Gram-negative and Gram-positive organisms may be different, we have been unable to differentiate the two clinically.

All cases of shock which were seen at the St. Louis City Hospital and the St. Louis University Hospitals between 1950 and January, 1956, were reviewed. There were 38 cases that fulfilled the clinical criteria of bacterial shock. These cases comprise the basis of this study.

The clinical criteria for establishing the diagnosis of bacterial shock in this study are as follows:

1. A systolic blood pressure less than 85 mm. of mercury accompanied by other signs of circulatory collapse. (One case did not fit these criteria. He was a known hypertensive patient whose pressure fell precipitously from 210/130 to 110/60 and who manifested all of the signs of peripheral vascular collapse.)

2. A positive blood culture obtained during the hypotensive episode.

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TABLE 1.—*Causative Bacteria*

Organism	Cases	Deaths	Male	Female	Age, Yr.
S. aureus	8	6	6	2	25-77
P. aeruginosa	8	5	5	3	45-88
A. aerogenes	3	1	2	1	52-84
S. albus	2	1		2	25-67
E. coli	6	5	4	2	48-85
Pneumococcus	3	2	2	1	48-64
Enterococcus	1		1		55
Proteus	5	3	4	1	50-85
Klebsiella	1	1		1	55
Mixed	1	1		1	31
E. coli S. aureus					
Total	38	25	24	14	25-88

Table 1 shows the causative organisms, age, sex distribution, and death incidence. From this Table it is apparent that, of the 37 cases due to a single organism, 14 were due to Gram-positive cocci and 23 were due to Gram-negative bacilli.

There were 24 male patients ranging in age from 44 years to 85 years. Fifteen of the twenty-four patients were over the age of 60 years. There were 14 women whose age ranged from 25 years to 75 years, and 5 were over 60 years of age.

The 38 patients presented a wide variety of symptoms and signs, with shock being the only universal finding. Eleven of the patients were comatose on admission, and reliable histories were not available. Tables 2 and 3 group the commoner findings which were present.

Rectal temperatures ranged from 94 to 107.4 F, with 27 of the 38 cases being febrile. Seven of the 11 comatose patients were febrile. Twenty-one patients had shaking chills. Sixteen patients were flushed. Fourteen were cyanotic. Sixteen were oliguric. Other less common findings were vomiting, headache, convulsions, jaundice, and melena.

A review of the significant laboratory findings revealed that all of the patients had positive blood cultures, as mentioned previously. The white blood cell count ranged from 150 to 72,000, with a median of 22,000. The ranges encountered with the causative organism are shown in Table 4. Thirty-three cases had a moderate to marked shift in the Schilling differential to the left.

The hemoglobin values ranged from 5 to 17 gm., three patients having less than 10 gm.

Thirty-two patients had plasma sodium, potassium, chlorides, and carbon dioxide determinations while they were in shock. Seventy-five per cent of these had a metabolic acidosis of varying degrees, the majority being mild. The others had values within normal limits (Table 5).

TABLE 2.—*Clinical Picture*

Organism	Cases	Shock	Rectal Temp. F	Chills	Oliguria	Coma	Vomiting
S. aureus	8	8	96.4-107	4	2	1	2
P. aeruginosa	8	8	103-107	8	1	2	2
A. aerogenes	3	3	97.6-104	0	2	0	0
S. albus	2	2	99-104	1	1	..	2
E. coli	6	6	94-104	1	4	2	2
Pneumococcus	3	3	103-104	1	3	3	..
Enterococcus	1	1	103	..	..	..	..
Proteus	5	5	100-107.4	5	2	2	1
Klebsiella	1	1	103	..	1	1	..
Mixed	1	1	100	1	..	..	..
Total	38	38	94-107.4	21	16	11	9

TABLE 3.—*Clinical Picture*

Organism	Cases	Cyanosis	Convulsions	Headaches	Jaundice	Flushed	Melena
S. aureus	8	4	..	3	1	4	..
P. aeruginosa	8	2	1	1	..	4	..
A. aerogenes	3	..	..	1	2	..	1
S. albus	2	1	1	..	..	1	..
E. coli	6	2	2	..	2	4	1
Pneumococcus	3	3	1	..	1	..	..
Enterococcus	1	..	..	1	..	1	..
Proteus	5	2	..	..	..	2	..
Klebsiella	1	1	..	..	..	..	..
Mixed	1	..	1	..	..	..	..
E. coli S. aureus							
Total	38	15	6	6	6	16	2

TABLE 4.—*White Blood Cell Count*

Organism	Cases	WBC
1. S. aureus	8	8,200-51,000
2. P. aeruginosa	8	500-42,000
3. E. coli	6	5,400-29,200
4. Proteus	5	20,000-34,700
5. A. aerogenes	3	22,000-72,000
6. Pneumococcus	3	11,500-27,000
7. S. albus	2	16,000-26,000
8. Enterococcus	1	30,000
9. Klebsiella	1	150
10. Mixed	1	40,000
E. coli		
S. aureus		
Totals		

5 — less than 10,000
18 — more than 20,000
5 — more than 40,000
13 survivors had counts ranging from 8,200 to 40,000

TABLE 5.—*Blood Chemistries in Thirty-Two Patients*

Electrolyte	Cases	Values mEq./L.
Sodium	13	138-145
	19	126-137
Chloride	10	98-100
	22	78-98
Potassium	21	4.2-5.5
	10	3.0-3.6
	1	6
CO_2	8	24-30
	12	19-22.5
	9	15-18

Electrocardiograms were done on 14 patients; 5 were interpreted as showing a sinus tachycardia; 3, as atrial fibrillation, and 1, as a myocardial infarction. The remaining five electrocardiograms were interpreted as normal.

Table 6 shows the various portals of entry of the bacteria into the blood stream, listed according to causative organism and therapeutic result. There were 16 bacteremias introduced via the genitourinary system, 11 of which followed urethral manipulation. Six of these cases were due to P. aeroginosa and five to P. vulgaris; E. coli was responsible for three cases. One case was caused by A. aerogenes, and one, by enterococcus. In 8 of the 16 cases originating from the genitourinary tract the patients survived.

TABLE 6.—*Portal of Entry*

Organism	Unknown	Genitourinary Tract	Biliary Tract	Uterus	Respiratory Tract
S. aureus	2*/2		1/0	1/0	2/0
P. aeruginosa	2/0	3/3			
A. aerogenes	0/1	0/1	1/0		
E. coli	1/0	2/1	2/0		
S. albus	1/1				
Enterococcus		0/1			
Pneumococcus					2/1
Proteus		3/2			
Klebsiella					1/0
Mixed				1/0	
E. coli					
S. aureus					
Deaths	6	8	4	2	5
Living	4	8	0	0	1

*Numerator indicates number dead; denominator, number living.

The portal of entry in six cases was the respiratory tract. Three of these were due to pneumococcus, two to aureus, and one to Klebsiella. Five of these six cases died, the survivor being a case of pneumococcal lobar pneumonia. The biliary tract was the portal of entry in four cases. E. coli was responsible for two of these cases, S. aureus for one, and A. aerogenes for one. All four of these cases died. One case was caused by S. aureus, and one case was due to a mixed infection of S. aureus and E. coli originating in the uterus. Both were fatal.

In 10 cases the portal of entry could not be determined. Four of these were due to S. aureus, two cases were due to S. albus, two were due to P. aeruginosa, one case was caused by E. coli, and one, by A. aerogenes. Of these 10 cases in which portal of entry could not be determined, 6 died.

Table 9 illustrates which antibiotics the survivors received. There were no significant differences in therapy between the survivors and nonsurvivors. Penicillin dosage ranged from 2,500,000 to 20,000,000 units daily. Streptomycin was given in 1 to 2 gm. daily dosage, and the other antibiotics were given in the usually recommended dosages.

Methoxamine (Vasoxyl) was used in nine patients. Eight had no response, and the ninth had a rapid elevation of blood pressure to normal levels.

Levarterenol (Levophed) bitartrate was used in 26 patients in an effort to elevate the blood pressure. Twenty-one cases had

TABLE 7.—*Data on Twenty-Four Male Patients*

Age	Probable Precipitating Factors	Blood Culture	Complicating Disease	Outcome
85	Uncertain; had difficulty starting stream	Pseudomonas	None known	Died
85	Pulled out Foley catheter	Proteus	Convalescing fractured hip	Died
85	Unknown	E. coli	Bronchopneumonia	Died
83	Transurethral resection	Proteus	None	Died
77	Cholangitis	S. aureus	Obstructive cholangitis	Died
71	Traumatic catheterization	E. coli	Multiple myeloma	Died
70	Unknown	Pseudomonas	Pharyngeal neoplasm; leucopenia 2 degrees HN_2	Died
68	Traumatic catheterization	E. coli	Pyelonephritis	Died
67	Unknown	S. aureus	Diabetes; perirenal abscess	Died
57	Unknown; lobar pneumonia	Pneumococcus	Pneumonia & meningitis	Died
57	Infected osteomyelitis	S. aureus	Compound infected fracture	Died
56	Unknown; bronchopneumonia	S. aureus	Bronchopneumonia	Died
84	Pulled out Foley catheter	Aerobacter	None known	Lived
83	Pulled out Foley catheter	Proteus	None known	Lived
67	Unknown; difficulty starting stream	Proteus	Cystitis	Lived
66	Pulled out catheter	Pseudomonas	Myocardial infarction	Lived
62	Difficulty starting stream	E. coli	Urethral stricture	Lived
61	Urethral dilatation	Pseudomonas	None known	Lived
55	Traumatic catheterization	Enterococcus	None known	Lived
52	None known	Aerobacter	None known	Lived
56	Cystoscopy	Pseudomonas	None known	Lived
48	Unknown	S. aureus	None known	Lived
48	Pneumonia	Pneumococcus	Pneumonia; cirrhosis	Lived
44	None known	S. aureus	None known	Lived

TABLE 8.—*Data on Fourteen Female Patients*

Age	Probable Precipitating Factors	Blood Cultures	Complicating Disease	Outcome
75	Suppurative pyelonephritis	Pseudomonas	Hydronephrosis with pyelonephritis	Died
73	Cholecystitis with lithiasis	Aerobacter	Cholecystitis with lithiasis	Died
67	Acute bacterial endocarditis	S. albus	Endocarditis	Died
64	Pneumonia	Pneumococcus	Pneumonia	Died
62	? liver biopsy	E. coli	Common-duct stone with cholangitis	Died
56	Suppurative pyelonephritis	Pseudomonas	Renal lithiasis with cholangitis	Died
55	Pneumonia	Klebsiella	Pneumonia	Died
53	Cholangitis	E. coli	Cholangitis	Died
50	Ureteral catheterization	Proteus	Calculus in l. ureter with suppurative pyelonephritis	Died
45	Unknown	Pseudomonas	Pancytopenia	Died
35	Pneumonia	S. aureus	Epilepsy, overwhelming aspiration pneumonia	Died
31	Septic abortion	S. aureus E. coli	Endometritis	Died
25	Septic abortion	S. aureus	Endometritis	Died
25	Uncertain	S. albus	Meningoencephalitis	Lived

an excellent response; five cases had a poor response.

Twenty-three patients received steroid therapy. Some received cortisone, some were given adrenal cortical extract, desoxycorticosterone, or corticotropin. Several patients received combined therapy.

All of the patients were given fluids, electrolytes, and blood if these were indicated.

Tables 7 and 8 show the precipitating factors (when these were known), results of the blood cultures, complicating disease (actually the bacteremia was often secondary to this process), and, finally, the outcome. It can be seen that only one of the 14 female patients survived, while 12 of the 24 male patients survived. There were 11 comatose patients, and 8 of these died.

TABLE 9.—*Thirteen Surviving Patients*

No. Patients	Antibiotic Treatment	Organism
3	Penicillin & streptomycin	S. albus, pneumococcus, Pseudomonas
3	Penicillin, streptomycin, & tetracycline (Achromycin)	Pseudomonas (2), Aerobacter (1)
2	Penicillin, streptomycin, & chlortetracycline (Aureomycin)	S. aureus and Proteus
1	Penicillin, streptomycin, & chloramphenicol (Chloromycetin)	E. coli
1	Penicillin, streptomycin, & erythromycin	S. aureus
1	Penicillin, streptomycin, & oxytetracycline (Terramycin)	Proteus
1	Penicillin, tetracycline, & chloramphenicol	Enterococcus
1	Chloromycetin, streptomycin, & sulfisoxazole (Gantrisin)	Aerobacter

Comment

Thirty-eight cases of bacteremias accompanied by peripheral vascular collapse are presented. The clinical picture was exceedingly variable. Most often the patient presented signs and symptoms of acute infections in various organ systems, e. g., chest, genitourinary tract, and biliary tract, and the bacteremia was belived to be secondary to these processes. However, in 10 cases no obvious focus of infection could be determined.

Sixteen patients were flushed, and most of the other twenty-two were cold and clammy to touch. It is of interest that the two patients exhibiting the extremes of temperature (94 F and 107.4 F) both survived. Waisbren described similar results in a series of 29 bacteremias due to Gram-negative rods. Thirteen of these had a so-called "toxic" picture and were normotensive, hot, dry, and flushed. Fifteen patients had a shock-like picture, with the signs and symptoms of circulatory collapse.[10]

There is no apparent difference in the organisms' ability to produce one or the other picture, as this probably depends upon the susceptibility of the host.[10] Perhaps this reflects previous sensitization with the offending bacteria with subsequent infections precipitating anaphylactic-like shock states. Spink has shown that the lethal toxin from staphylococci which is antigenic may produce circulatory failure.[15]

The laboratory findings generally were consistent with a severe infection. All but five patients had white blood cell counts greater than 10,000, and 18 had counts greater than 20,000. Of the five cases whose counts were less than 10,000, one was 150 and one was 500, both representing leukopenias secondary to mechlorethamine hydrochloride (nitrogen mustard) therapy, which was given for malignancies. The three remaining cases with white blood cell counts of less than 10,000 were 5400, 8200, and 8500. Five patients had more than 40,000 white blood cells, and these were infections with A. aerogenes (two), S. aureus, P. aeruginosa, and the one patient with a mixed infection—E. coli and S. aureus. The 13 surviving patients had counts ranging from 8200 to 40,000.

As was noted above, only three patients had hemoglobin values of less than 10 gm., and all of these died. Of the 13 survivors, 12 had more than 13 gm. of hemoglobin. Ebert[3] observed that a small hemorrhage (1% of the body weight) caused a markedly exaggerated fall in blood pressure and cardiac output following the administration of endotoxin.

The plasma electrolytes were determined in 32 of the 38 cases, and the majority showed a mild metabolic acidosis. There were no significant differences in the electrolytes between the survivors and nonsurvivors.

From Table 8 it can be seen that 13 of the 14 women had foci of severe infections which gave rise to the bacteremias, and all of these patients died. The one surviving woman had a S. albus meningoencephalitis secondary to a bacteremia. The portal of entry could not be established.

In contrast to this, 13 of the 24 male patients had no apparent infection at the site of entry, or this site could not be determined. Ten of these thirteen survived. The three deaths occurred in men whose ages were 85 years, 85 years, and 83 years. The other two male survivors had foci of mild infections; one had pneumococcal pneumonia, the other a cystitis due to P. vulgaris.

After further analysis it became apparent that the patients who died had either very marked inflammatory reactions at the portal of entry or severe complicating diseases, or were otherwise poor risks.

It was not possible to ascertain the effects of much of the therapy used. Large doses of antibiotics were used in all of the patients. Antibiotic therapy was instituted before the organism was identified and before sensitivity could be determined.

Blood, fluids, and electrolytes generally failed to have noticeable effect, and the only vasopressor agent which gave satisfactory

results was levarterenol. This was used in dosages varying from 4 to 48 mg. per 1000 cc. of fluid and was given intravenously at rates which would maintain the systolic blood pressure around 120 mm. of mercury. It was used continuously for as long as five days, but generally could be discontinued after 18 to 24 hours. Levarterenol often raised the blood pressure when other measures failed. Others have reported similar results.[11,16,17] Ebert successfully raised blood pressure with this drug after experimental endotoxin-produced shock.[3]

The results of steroid therapy were difficult to evaluate. Of the 23 patients who were given steroids, various dosages and combinations of them were given with periods of administration ranging from several hours to three days. Of these 23 patients, 15 died and 8 lived. Thus, of the 13 survivors in this study, 8 received steroid therapy. We are unable to determine from these results whether steroid therapy exerted any beneficial effects.

Cortisone given to dogs prior to the administration of endotoxin had no effect in preventing shock.[3] However, there is some experimental evidence which shows that response to steroids varies with the time at which treatment is initiated,[18] and that, if given early, may effectively prevent shock. It is of interest that two of our cases were being given hormones at the time of shock. Hall and Gold report that one of four patients who received steroids recovered. However, they comment that this cannot be ascribed solely to the steroid therapy and that steroid therapy did not seem to lessen shock.[11] It is the opinion of some authors that cortisone has an antitoxin effect which should be beneficial in treating bacterial shock. It is also reasonable that some cases may be accompanied by adrenal cortical insufficiency, and here, of course, steroids may be helpful.[19-21]

Summary

Thirty-eight cases of bacterial shock are presented. Twenty-three of these cases were due to Gram-negative bacilli and fourteen cases, to Gram-positive cocci, one case being due to a mixed infection. The variable clinical and laboratory findings are emphasized. The commonest portal of entry was the genitourinary tract following urethral manipulation.

Of the 23 cases which were associated with severe inflammatory diseases at the portal of entry, 22 died, while, of the 15 that had no marked infection at the portal of entry, 3 died. It is our opinion that the degree of inflammation at the portal of entry is an important factor in survival.

Therapy is difficult to evaluate. Large doses of antibiotics and vasopressor materials should be given at once.

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Acute Benign Idiopathic Pericarditis

A Report of Twenty Cases

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Pericarditis has usually been thought to be synonymous with serious underlying disease. In the past decade clinicians have become increasingly aware of a relatively benign inflammatory disease involving the pericardium without any known specific etiological agent. In a two-year span on a cardiac service in the Army, 20 cases of so-called idiopathic benign pericarditis were encountered, and a detailed analysis of these cases will be presented along with the differential diagnosis and prognosis.

Since the introduction of antibiotic therapy, it has been our belief that the disease makes up a higher percentage of pericarditis than was formerly reported. Reeves,[1] in 1953, reported that acute benign pericarditis constituted 10.4% of 108 cases of pericarditis; however, many of these occurred in the preantibiotic era. Part of this discrepancy may occur from the relative age and sex difference between Army and civilian hospitals.

In 1854, Hodges[2] initially described a case of benign pericarditis occurring in a 40-year-old domestic worker. There was no association with any of the usual causes of pericarditis, and it was followed by a rapid recovery without any specific form of therapy. Prior to the turn of the century, numerous other reports[3-7] were published, revealing widespread appreciation of the existence of this syndrome. In 1942, Barnes and Burchell[8] first crystallized this syndrome in the American literature.

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Etiology

At present the cause of benign pericarditis is unknown. To date multiple attempts at culturing pericardial fluid[9-12] have established the fact that there are no culturable organisms. Numerous serologic tests[13-15] have failed to reveal any specific infectious agents. Some other authors believe[9,16] it may be viral in origin, but no specific viruses have been isolated. Its occurrence during the course of primary atypical pneumonia has been well established.[17-19] Certain authors have noted a similarity between this disease and the hypersensitivity phenomenon, pointing out the preceding upper respiratory infection with the latent period.[10, 20,21] More recently acute benign pericarditis has been thought to be due to allergy[22] and serum sickness.[23] It might be stated as Werther[24] and others[8] have noted that it is a syndrome probably due to a variety of causes, that it is inflammatory in nature and may be infectious in origin, and that in some instances it is quite closely allied to the diseases of hypersensitivity. In other instances it may fairly closely simulate the postcommissurotomy syndrome.

Symptomatology

The outstanding feature of pericarditis is the pain, which closely simulates that of myocardial infarction, which occurred in all of our 20 cases. It was predominantly substernal in nature and was exaggerated by inspiration, lying down in the recumbent position, "burping," and swallowing. At times it was described as crushing, sharp, stabbing, or sticking in nature. In some

TABLE 1.—*Symptomatology—Twenty Cases*

Pain	No. Patients	Per Cent
Substernal	20	100
Exaggerated on inspiration	20	100
Exaggerated in recumbent position	18	90
Sharp stabbing	12	60
Radiation to neck and arms	9	45
Exaggerated by breathing	3	15
Exaggerated by swallowing	3	15
Radiation to both shoulders	3	15
Pain always in left chest	2	10
Crushing pain	1	5
Antecedent upper respiratory infection (ranging 3-7 days)	1	5
	10	50

there was radiation to the shoulders, neck, or arms.

Christian [25] had noted that elevation of the sphygmomanometer cuff on the arm at times exaggerated the pain. He also recorded that palpation of the epigastrium and exertion of pressure on the upper abdomen would exaggerate the discomfort. He has noted that frequently the pain centered near the left shoulder at a place about half way between the base of the neck and the left shoulder.

Carmichael [26] found a similar type of pain, and in addition he noted that it frequently radiated into the costal margin, back of the neck, jaw, elbows, and right chest.

Carmichael [26] noted that frequently associated with the pain there were other symptoms, such as malaise, fever, cough, dyspnea, anorexia, chills, orthopnea, and vomiting, which were the commonest manifestations. More rarely palpitations, ankle edema, night sweats, headaches, cyanosis, and insomnia have been observed.

Antecedent upper respiratory infections were noted to occur three to seven days before the onset of the pain in half of our patients, and similar observations have been made by Carmichael,[26] Barnes and Burchell,[8] and Goyette.[11]

TABLE 2.—*Time of Appearance and Duration of Friction Rub*

	No. Patients	Per Cent
Time of Appearance		
6th hr.	4	20
24th hr.	8	40
2d day	6	30
3d day	1	5
10th day (after tap)	1	5
Duration		
6th hr.	3	15
1st day	2	10
3d day	2	10
7th day	1	5
10th day	2	10
12th day	1	5
14th day	2	10
Undetermined	7	35

Physical Findings

The outstanding cardiac finding of the disease is the appearance of a friction rub. This was recognized in all 20 of our cases; in 65% it was to-and-fro in character, and in 35%, systolic only. It has an early onset and is rather evanescent but sometimes persists up to 14 days.

Pericardial rubs may present as a noisy, squeaking, or crunching sound heard over the sternal area, and they continue when the patient holds his breath. They may occur slightly late in systole and diastole, when it is thought by Wood [27] that the surface of the heart moves rather than the blood. Moving the patient about may alter the intensity of the rub.

TABLE 3.—*Duration of Fever*

Days	No. Patients	Per Cent
0-2	1	5
2-4	10	50
4-6	5	25
6-8	2	10
8-10	1	5
10-16	1	5

A paradoxical pulse was present in 5 of our 20 cases. Pleural friction rubs were heard in six. Decreased cardiac sounds were noted in some of the patients with marked amounts of pericardial fluid. Ewart's sign with compression of the left lower lobe of the lung was not encountered. Auenbrugger's sign with downward rotation of the dome of the liver was not seen.

Fever was found to be present in all of our cases, and it was predominantly defervescence by lysis in 18 of the 20 cases. Peaks of 101 to 103 F were most frequently encountered, and in only one was the temperature seen to be elevated over 103 F; this patient had 104.2 F. The average duration can best be noted in Table 3.

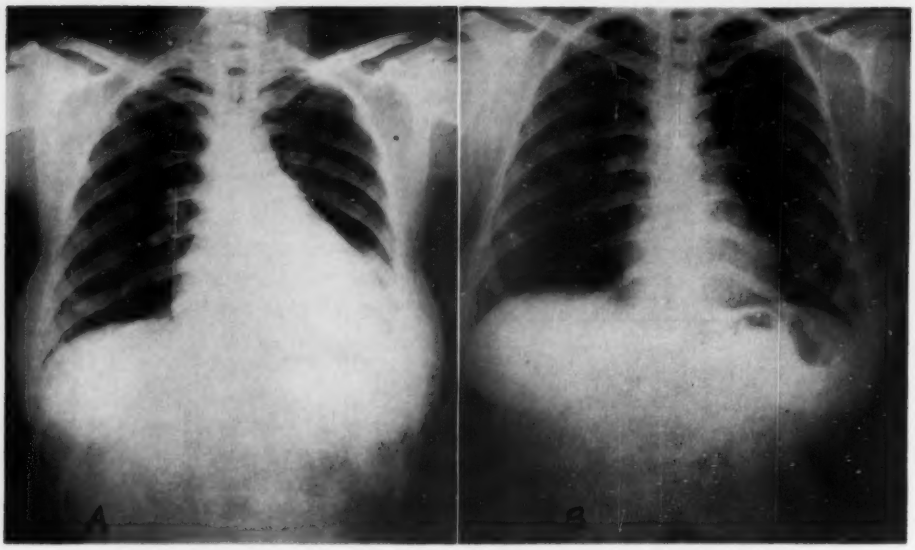

Fig. 1.—Teleroentgenograms. *A*, typical pericardial effusion. *B*, normal cardiac silhouette after effusion has spontaneously disappeared.

Teleroentgenograms (Fig. 1)

There is a majority opinion that there is an enlarged cardiac shadow in most of the patients with acute benign pericarditis. Levy and Patterson [9] state that it is probably due to dilatation of the heart, and they noted this enlargement in 16 of 25 cases observed by them. Carmichael [26] observed an enlarged cardiac shadow in 25 of his 50 cases. He believed it was primarily due to myocardial dilatation, rather than effusion, because of a lack of suppression of cardiac sounds, the absence of signs of cardiac compression, and the persistence of a normal voltage on the electrocardiographic tracing.

Williams and Steinberg [28] noted that enlargement of the cardiac silhouette was most marked in the transverse diameter, with distortion of the posterior inferior recess and foreshortening of the vascular shadow. They thought it was most evident in the recumbent or Trendelenburg position, with a rapid change in shape and size of the silhouette with widening of the superior mediastinal shadow. Diminished pulsations of the cardiac borders on fluoroscopy may be of aid in determining its presence. Besterman and Thomas [29] have agreed with this and have also noted that occasional compression collapse of the left lower lobe of the lung results. With the use of radiopaque catheter tip against the right atrial wall, the observed distance between it and the edge of the cardiac outline may aid in differentiating the conditions. Furthermore, this can be better delineated by the use of a small amount of iodopyracet (Diodrast) released through the catheter. Williams and Steinberg,[28] using iodopyracet, have noted that the opacified right and left cardiac chambers seem to be well within the cardiac silhouette, while the intervening space represented the chamber walls and the fluid within the pericardial sac, and they had pericardial taps to prove it.

Enlarged cardiac silhouettes were noted in 14 of our 20 cases, and definitely demonstrable fluid was noted by positioning (Trendelenburg) in five of these patients. However, some diminution in pulsation on fluoroscopy was noted in the majority of these. It is our belief that the enlargement of the cardiac silhouette in the majority is probably due to the presence of pericardial

TABLE 4.—*Teleroentgenogram*

	No. Patients	Per Cent
Enlarged cardiac silhouette	14	70
Demonstrable fluid by positioning (Trendelenburg)	5	25
Associated pleural effusion	3	15
Associated local infiltration—bases	3	15

effusion. The rapidity of the changing size seems to favor this concept, in our opinion.

Electrocardiographic Tracings (Figs. 2 and 3)

As noted by Carmichael,[26] the electrocardiographic changes depend upon the phase in which the pericarditis is first observed, the degree of the subepicardial injury, the amount of pericardial effusion, and the adequacy of electrocardiographic exploration. RST-segment elevations were observed in 19 of our 20 cases, and the majority of them occurred early and persisted for 48 to 72 hours.

Goldman[30] has noted that the RST-segment elevation may be normal, especially in young Negroes, up to 2-4 mm. in Leads V_3 to V_6, with normal elevations ranging from 0 to 2.0 mm. in V and V_2. With the use of the Masters 2-step exercise test we have been able to note, as have others,[6] that the RST segment returns to the isoelectric line immediately following exercise but that with acute pericarditis it does not change. We have observed this phenomenon in nine normal cases, eight of whom were Negroes.

The RST-segment elevations were then followed by T wave inversions in the corresponding leads in which the RST segments had previously been elevated. The majority of these had returned to normal in less than a month, but in three they were seen to persist up to three months. This is very helpful in the differentiation from tuberculous pericarditis, in which T waves remain inverted for longer periods of time and sometimes permanently.

TABLE 5.—*Electrocardiographic Findings in Twenty Cases*

	No. Patients	Per Cent
Persistence of RST segment elevations	19	95
48 hr.	2	10
4 days	1	5
5 days	3	15
6 days	4	20
7 days	4	20
8 days	2	10
9 days	1	5
12 days	1	5

Levy and Patterson[9] have never observed a prolonged P-R interval with acute benign pericarditis, and this is very helpful in the differentiation from rheumatic fever. We likewise have not encountered this. They did observe, however, three patients with transient rhythm disturbances, which we have not.

Laboratory Findings

The majority of the laboratory tests, exclusive of electrocardiographic tracings and teleroentgenograms, are of value in a negative way. In Levy and Patterson's cases[9]

TABLE 6.—*T Wave Inversion*

Returned to Isoelectric Level in	No. Patients	Per Cent
7 days	2	10
14 days	6	30
21 days	3	15
24 days	4	20
28 days	1	5
35 days	1	5
12 wk.	3	15

antistreptolysin titers were determined 25 times in 16 cases, and in 22 of these determinations they were below 200, which is an insignificant level. These results are helpful in ruling out acute streptococcic infections suggestive of the etiological agent in rheumatic fever. In 14 of our cases in which they were tested, insignificant levels were found to exist in all of them. Tuberculin skin tests, first and second strengths, are valuable when negative and were found to be negative in 17 of our 20 cases, aiding in the differentiation from tuberculosis. C-reactive proteins were negative in 90% of the 10 cases which were tested in our series, aiding in partially ruling out acute rheumatic fever.

Leukocyte counts in the majority are increased to levels between 10,000 and 25,000, with a rather marked increase in the polymorphonuclear neutrophil ratio.

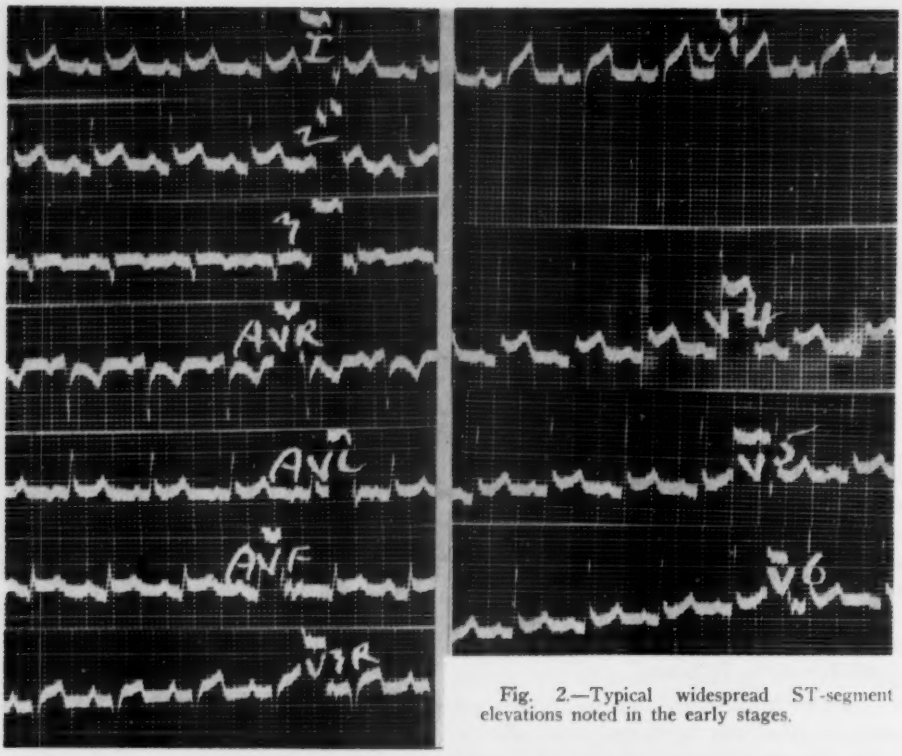

Fig. 2.—Typical widespread ST-segment elevations noted in the early stages.

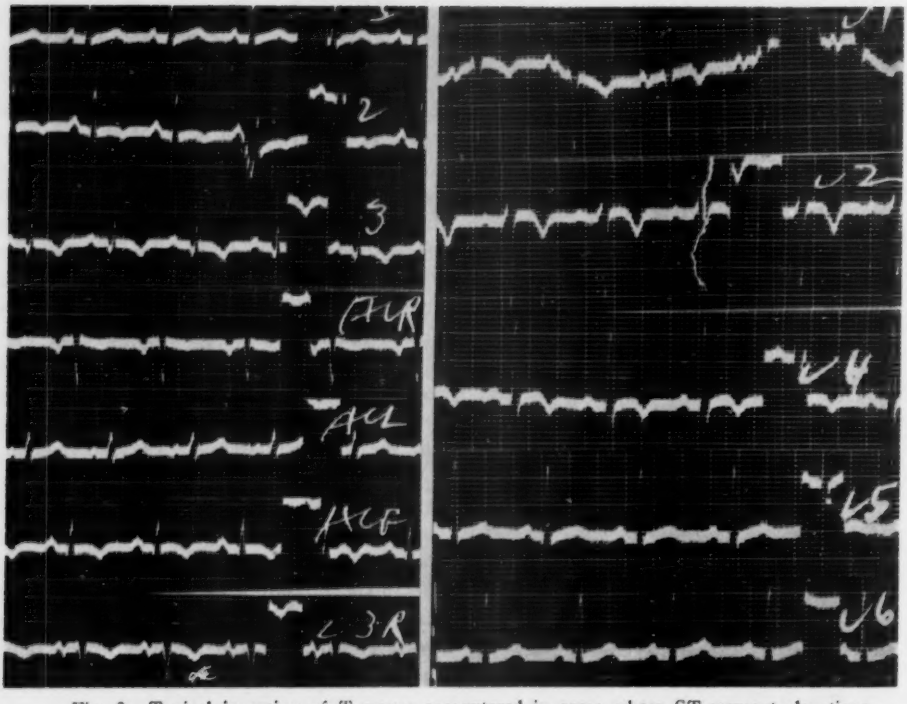

Fig. 3.—Typical inversion of T waves encountered in areas where ST-segment elevations were previously noted.

TABLE 7.—*Laboratory Findings*

Leukocyte Counts	No. Patients	Per Cent
5,000-10,000	4	20
10,000-15,000	4	20
15,000-20,000	9	45
20,000-25,000	2	10
25,000-30,000	1	5
Polymorphonuclear Neutrophils, per Cent		
65-70	2	10
70-75	1	5
75-80	2	10
80-85	7	35
85-90	7	35
90-95	1	5

The sedimentation rate is of importance in following the progress of the disease. It tends to furnish valuable information regarding the duration of the activity. It was found to be elevated in all 20 of our cases and remained so for from one to six weeks, with the average elevation being maintained until the fourth or fifth weeks.

Examination of the fluid obtained from the pericardium is uncommon because the majority of them spontaneously regress without tapping. In some of these patients in whom it has been done, for example, in Levy and Patterson's series,[9] the fluid has been found to be straw-colored, with specific gravity ranging from 1.015 to 1.022 and cell counts up to 2000 per cubic milliliter, with monocytes predominating and no organisms cultured.

Differential Diagnosis

The more commonly encountered cardiac conditions which especially need to be differentiated might include rheumatic fever, tuberculosis, coronary thrombosis, and normal RST-segment elevations. Less commonly, pyogenic, neoplastic, uremic, and collagen diseases and coccidiomycosis and cholesterol pericarditis may be encountered.

Tuberculous pericarditis is characterized clinically [31] by an insidious onset, with a dull aching vaguely localized pain frequently accompanied by pleural effusion. Tuberculin skin tests are positive in the majority of these patients. Electrocardiographic tracings may also reveal P-R or QRS abnormalities, as well as ST and T wave and Q-T changes. A fairly specific response to salicylates or the steroids may also be noted as an aid in its delineation.

Coronary occlusions are frequently encountered in a little older age group and are frequently accompanied by a shock-like picture, arrhythmias, acute failure, or other complications not seen with acute benign pericarditis. Electrocardiographic tracings reveal reciprocal ST changes in the standard and unipolar limb leads, and ultimately Q waves develop in the involved areas. Serial electrocardiographic tracings are most helpful in differentiating these two conditions.

Goldman [30] has noted that in normals the RST-segment elevation may be present in V_1 to V_6 in varying amounts, but they show none of the other clinical manifestations of pericarditis. In addition, the Masters 2-step exercise test returned them to normal, unlike its effect on pericarditis, where no change is observed. We have seen nine cases in which the RST segments have been elevated in normal persons and have noted their return to the isoelectric levels in eight of the patients on exercise.

Coccidioidal pericarditis [33,34] has a predilection for certain geographical areas in the United States and is more prevalent in Negroes and Filipinos. Frequently the x-rays will reveal an associated pneumonitis. Erythema nodosa may be present. Skin tests may be positive 10 to 45 days after exposure or 2 to 21 days after the onset of the disease. Complement-fixation and precipitin tests may be of diagnostic help. Recovery of the organisms from the sputum or pericardial taps or tissue biopsy establish the absolute identity of the causative organisms.

TABLE 8.—*Laboratory Findings*

Sedimentation Rate	No. Patients	Per Cent
(Elevated in All 20 Cases)		100
1-2 wk.	2	10
2-3 wk.	2	10
3-4 wk.	5	25
4-5 wk.	8	40
5-6 wk.	2	10
12 wk.	1	5

The identity of the organism in pyogenic pericarditis may occasionally be noted with thoracotomy and biopsy if the more conventional approach of pericardial tap and culture proves unrevealing. Overwhelming infection within the thoracic cage or in the blood stream may be causative of it and may be accompanied by an extremely high leukocyte count.

Uremic pericarditis is seen at times terminally in severe renal disease with markedly elevated blood urea nitrogens. Neoplastic disease may be established as a causative factor in pericarditis by biopsy at the time of thoracotomy. The pericarditis seen to accompany collagen diseases, such as lupus erythematosus, periarteritis nodosa, or rheumatoid arthritis, is a specialized subject and entails many specialized diagnostic procedures to establish it adequately. Cholesterol pericarditis may be entertained as a possibility when an excessively high cholesterol content is found in the pericardial fluid at the time of pericardiocentesis.

Course and Prognosis

Levy and Patterson[9] experienced four recurrences in three of their patients. These were noted to occur even as late as 8 to 10 years after the original pericardial insult.

Freilich[35] reported on a patient in 1952 who had what appeared to be acute nonspecific pericarditis and subsequently developed constrictive pericarditis. Fluoroscopic studies in that patient after the fourth recurrence revealed a thick irregular and immobile left cardiac border. Electrokymography confirmed that finding. He postulated that 80% of constrictive pericarditis cases have unconfirmed etiology, and these may have resulted from acute benign idiopathic pericarditis.

Our experience fairly closely paralleled that of Goyette.[11,31] We had three patients who had recurrences, and these were of a milder nature and briefer duration than the initial episodes. The majority of our patients made a complete recovery in an average of three to five weeks. No specific type of therapy was given to any of these patients, and bed rest was the only adjunct. Goyette[36] stated he had never seen a patient develop constrictive pericarditis following acute benign idiopathic pericarditis. This also is in agreement with our observations.

We think that tapping is seldom indicated. In rare instances where cardiac tamponade ensues, or if there is a question as to a possible pyogenic or tuberculous pericarditis, it may be indicated for diagnostic purposes.

No rhythm disturbances were encountered in our series. Morris[37] had a patient with pericarditis who developed persistent ventricular tachycardia. This was successfully treated with the intravenous administration simultaneously of procaine and quinidine. Levy and Patterson[9] found 3 cases of transient arrhythmia in 27 cases of pericarditis.

Summary

A brief review of the literature with a report of an additional 20 cases of acute benign idiopathic pericarditis is presented. The history of an antecedent upper respiratory infection followed by sudden chest pain, closely simulating myocardial infarction, is noted. The appearance of a friction rub, characteristic electrocardiographic abnormalities, and a rapidly changing cardiac silhouette by x-ray aid in making the diagnosis. The course is usually brief with complete recovery, but recurrences are fairly common.

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Hypercalciuria Following Poliomyelitis

Its Relationship to Site and Degree of Paralysis

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Hypercalciuria and demineralization are frequent sequels to severe paralytic illnesses. Freeman [1] and many others * emphasized that osteoporosis and calcium-containing genitourinary calculi commonly complicate traumatic paraplegia. Excess calcium loss also may be inferred to occur in many patients with multiple sclerosis and polyneuritis, since calcium-containing stones often develop during these illnesses. Whedon and Shorr [2] recently demonstrated that every one of seven extensively paralyzed patients developed profound losses of calcium and phosphorus after poliomyelitis.

The studies cited above were all performed on patients suffering marked paralysis and immobilization. Except for Whedon and Shorr's investigation, they give relatively little quantitative data on serial patterns of mineral excretion. There are few data available to indicate whether, with paralysis, the intensity or duration of hypercalciuria bears any relationship to the site, degree, or extent of denervation. Few investigations have been directed toward determining whether nervous system illnesses produce decalcification in the absence of immobilization. This lack of analyses perhaps reflects a widespread assumption that demineralization, hypercalciuria, and genitourinary stone formation are a potential threat only in the presence of severe paralysis and immobility.

Patients with widely varying degrees of paralysis due to poliomyelitis were studied in the present investigation. Analyses of urinary calcium, phosphorus, and creatinine excretion were carried out during acute and convalescent illness periods lasting several months. Some of the subjects were almost completely quadriplegic and remained at bed rest for months, while others had little weakness except in bulbar innervated muscle groups and were in bed only a few days. Paralysis and immobilization ranged from mild to severe; it was, therefore, possible to determine whether any relationship existed between the extent and location of paralysis and the intensity and duration of subsequent abnormalities in calcium and phophorus excretion.

Procedure

Fifty-four males and females, including adults and children, were studied in the Northwest Respirator Center of the University of Washington for periods lasting from 1 to 12 months during acute and convalescent stages of poliomyelitis. Twenty-seven patients had studies which lasted at least six weeks, and the excretion patterns on this group form the basis for most of the present report (Table 1). Some patients were seen from onset of disease, while others were treated during convalescence only. All received medical and physical rehabilitative treatment for the direct effects and complications of poliomyelitis during the study period. Active and passive activities were introduced into the treatment program as early as possible in convalescence.

Daily calcium intake was restricted to and in most cases reached 500 mg. per day. Diets were otherwise unregulated. Total intake was urged to 2000 to 2500 Cal., and protein was kept above 75 gm. per day. Tube feedings were employed for patients who could not swallow because of pa-

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* See bibliography of Reference 25.

TABLE 1.—*Data on Studies of Twenty-Seven Patients*

	Patient	Age, Sex	Ht., Cm.	Wt., Kg.	Paralysis		Clinical Data	Respirator		Activity				Comment
					CR. N.	Peripheral		Full Time	Part Time	Passive Standing	Wheel Chair	Crutch Walking	Walking	
Mild bulbar paralysis														
	E. D.	22♀	62	51	9, 10	0	Very mild illness	0	0	3 days	--	--	3 days	Disch. 5 wk.; fully active
	J. Fr.	33♂	72	73	9, 10, 11	0	Mild hypertension unable to swallow 3 wk.	0	0	5 days	--	--	1 wk.	Disch. 6 wk.; teacher working 10 wk.
	P. B.	28♂	70	67	7, 9, 10	0	Very mild illness	0	0	3 days	--	--	3 days	Physician; disch. 2 wk.; working 3 wk.
Severe bulbar paralysis														
	T. Ch.	22♂	71	62.4	5, 7, 9, 10 encephalitic	Transient lt. triceps, R. peroneal	Mod. severe illness, diff. swallowing 3 wk.	0	0	8 wk.	3 wk.	--	8 wk.	Disch. 3 mo.; Residual 5, 7, 10.
	V. J.	4♂	40	26	5, 7, 9, 10, 11 encephalitic	Slight weak. neck flexors without residual	Severe illness, central resp. failure; tracheotomy tube, unable to swallow 4 mo.	2 wk.	0	5 wk.	--	--	7 wk.	Disch. 4 ½ mo.; temporary wt. loss 40% body wt.
	J. Bl.	7½♂	51	27	7, 9, 11, 10	Slight weak. left shoulder	Severe illness, central resp. failure, hypertension; tracheotomy, unable to swallow 9 wk.	3 wk.	0	6 wk.	8 wk.	--	10 wk.	Disch. 4 mo. to school
Bulbar upper spinal paralysis														
	A. W.	32♂	74	62	7, 10 encephalitic	Severe paralysis neck extensors, shoulders, and upper extremities	Severe illness, central resp. failure; tracheotomy and resp. acidosis and hypoxia 10 days	3 wk.	15 wk.	8 wk.	13 wk.	--	15 wk.	Disch. 7 mo.; fully ambulatory
	R. Fl.	32♂	73½	63	7, 9, 10, 11 encephalitic	Mod. paralysis neck and rt. shoulder	Severe illness, central resp. failure; tracheotomy, unable to swallow 4 wk.	2 wk.	5 wk.	5 wk.	--	--	9 wk.	Disch. 3 mo.; working 6 mo.; 3d. wk. 24-hr. urine: 11-oxysteroid, 102 mg.; 17-ketosteroid, 44 mg.

TABLE 1.—*Data on Studies of Twenty-Seven Patients*—Continued

	Patient	Age, Sex	Ht., Cm.	Wt., Kg.	Paralysis		Clinical Data	Respirator		Activity				Comment
					CR. N.	Peripheral		Full Time	Part Time	Passive Standing	Wheel Chair	Crutch Walking	Walking	
Moderate scattered paralysis	M. L.	28♀	64.5	46	0	Mod. paralysis shoulders, both legs, slight weakness back	Mod. severe illness	8 days	2 wk.	7 wk.	4 wk.	10 wk.	12 wk.	Transf. 2½ mo.
	L. K.	22♀	62	46	10 (mild)	Mod. paralysis shoulders, lt. hip and knee; slight parsl. trunk, rt. knee	Mild illness	7 days	8 wk.	11 wk.	12 wk.	13 wk.	25 wk.	Disch. 7½ mo.; housewife
	E. W.	28♀	62	60	9, 10 enceph-alitic	Shoulders slight, rt. hip mod. mild gen. weakness	Onset postpartum; mod. severe illness; unable to swallow 4 wk.; tracheotomy and coma	17 days	8 wk.	11 wk.	12 wk.	15 wk.	24 wk.	Transf. 20 wk.; home 6 mo.; housewife
	R. Ra.	28♂	70	76	0	Mod. hips, both shoulders	Mod. illness with central resp. failure	10 days	2 wk.	6 wk.	7 wk.	--	--	Transf. 10th wk.
	F. L.	20♂	62	63 ↓ 32.5	5, 7, 9, 10, 11, 12 enceph-alitic	Both shoulders mod.; lt. hip mod.; upper trunk slight; lt. diaphragm	Severe illness with 4½ mo. swallowing diff.; permanent tracheotomy and permanent central resp. failure	14 wk.	13 mo.	18 wk.	15 wk.	--	36 wk.	Repeated convalescent complications; Lost 50% body weight; disch. 14 mo.; unemployed
Lower spinal paralysis	H. W.	36♀	61	36	0 enceph-alitic	Motor and sensory paraplegia; slight loss rt. shoulder; full crutch walker	Mod. severe illness; tracheotomy	4 wk.	10 wk.	2 mo.	--	5 mo.	--	Resistant bladder infection, T.U.R.; disch. 8 mo.; housewife
	M. S.	33♀	62	61	7, 9, 10	Rt. arm and diaphragm mod. weak; paraplegia complete	Mod. severe illness with 10 days swallowing diff.; prev. Tbc. on INH; tracheotomy	12 days	6 wk.	12 wk.	14 wk.	--	--	Disch. 6 mo.; housewife
	D. Ba.	28♀	60	83 ↓ 67	7, 10	Mod. shoulders; total paraplegia; crutch walking prevented by obesity	Mod. illness 10 days; swallowing difficulty with tracheotomy	3 wk.	12 wk.	4-6 mo. irreg.	14 wk.	--	--	Recurrent thrombophlebitis; disch. 11 mo.; housewife
	H. B.	36♂	69	74 ↓ 63	5, 7	Old amputation lt. knee; shoulders mod.; trunk good; total paraplegia	Mod. severe illness; tracheotomy and 5 wk.; swallowing diff.; central resp. failure; early resp. infection	8 wk.	10 mo.	49 wk.	36 wk.	--	--	Disch. 14 mo.; unemployed
	R. H.	16♂	70	59	0	Transient diaphragmatic paresis but total paraplegia	Mod. severe illness, pseudohyperparathyroidism; hypertension; Ca, 18 mg.; P, 3 mg.;	5 wk.	12 wk.	16 wk.	18 wk.	22 wk.	--	Adm. 14 wk.; disch. 9 mo.; school boy
	J. Bo.	28♂	72	73	Mild 10, 12	Slight shoulders; paraplegia save for mod. left hip	Mild illness	8 days	8 wk.	7 wk.	--	--	--	Transf. 8 wk.

Severe diffuse paralysis	K. H.	16♀	63	41	0 encephalitic	Total quadriplegia with mod. sparing resp. accessories	Severe illness, severe hypertension, papilledema	2½ mo.	Permanent	15 wk.	4½ mo.	..	..	Disch. 9 mo.; invalid
	S. W.	17♀	60	36	7, 9, 10, 11 encephalitic	Total quadriplegia and trunk paralysis	Severe illness; 3 wk. swallowing ing diff.; tracheotomy; convalescence diff. marked by autonomic instability	14 mo.	Permanent	..	8 mo.	..	..	Disch. 1 yr.; invalid
	O. K.	23♀	62	60	0	Quadriplegic save poor forearms; adequate vital capacity	Mod. illness; severe anxiety; papilledema and hypertension; early convalescence	1 wk.	8 wk.	..	13 wk.	..	..	Disch. 7 mo.; housewife
	R. O'C.	22♂	71	42	9, 10 encephalitic	Total quadriplegia and trunk paralysis save lt. forearm; functional accessories for breathing	Mod. severe illness; tracheotomy, 2 wk. swallowing; atelectasis and repeated resp. infections early convalescence	6 mo.	Permanent	33 wk.	28 wk.	..	..	Adm. 6 mo.; disch. 14 mo. retraining at home
	J. E.	28♂	72	58	0	Total quadriplegia and severe trunk paralysis; adequate assessories for breathing	Mod. illness	8 wk.	Permanent	..	33 wk.	..	..	Adm. 8½ mo.; disch. 13 mo.; invalid
	R. Re.	33♂	71	58	0	Total quadriplegia and trunk paralysis save rt. hand; adequate accessories for breathing	Mod. illness	8 wk.	Permanent	14 wk.	13 wk.	..	..	Adm. 10 wk.; disch. 6 mo.; invalid
	D. O'C.	28♂	72	71	10 (mild)	Quadriplegia save left forearm, rt. hand; mod. upper trunk; adequate vital capacity	Mod. illness	3 wk.	6 wk.	12 wk.	16 wk.	..	..	Adm. 6 wk.; disch. 10 mo.; lawyer; to work

ralysis. Fluids were forced, and daily urine outputs varied between 1500 and 3000 cc.

Twenty-four-hour urinary calcium, phosphorus, and creatinine excretion was measured for periods indicated in Tables 2 through 7. Nurses were trained in collection techniques, and total 24-hour urine outputs were collected under toluol on all subjects on Monday through Thursday of each week. A few specially instructed patients continued to collect 24-hour urine samples after they had been discharged from the hospital. Urine aliquots were taken after a thorough shaking of each refrigerated specimen, and four-day collections were quantitatively pooled. If individual specimens were lost or the accuracy of collection was doubted, the entire specimen was discarded. The constancy of creatinine excretion was used as a guide to the accuracy of collections. All urines were analyzed for calcium,[3] phosphorus,[4] and creatinine[5] by standard methods. Serum calcium, phosphorus, and alkaline phosphatase were analyzed periodically on all patients.

Routine urinalyses were done weekly. Excretory urograms were performed on all patients at three and six months after illness. Except where designated, no patient developed signs, symptoms, or roentgenographic evidence of renal calculi.

Normal values for maximal daily urinary calcium output were estimated at 250 mg. for men, 160 mg. for women, and 80 mg. for children. The values for men were taken from the data of Nicolayson et al.,[6] those for women and children, from Knapp.[7] Random 24-hour urine samples taken on healthy volunteers and analyzed in this laboratory always showed urinary calcium excretion well below these maximal values, with an average on an uncontrolled diet of 190 mg. per day of calcium for males and 110 mg. per day of calcium for females.

Results

I. Calcium Excretion.—A. Mild Bulbar Paralysis (Table 2, Fig. 1): Proof of poliomyelitis infection in the three adults in this group was gained by isolation of virus from the stool. Paralysis was confined to muscles innervated by cranial nerves. No patient had respiratory distress, none were severely ill, and all were up and walking about the ward by the end of the first week. One patient had paralysis of deglutition requiring tube feeding for three weeks, the other two were able to swallow. Clinical data on these and the other patients in the study are summarized in Table 1.

Urinary calcium excretion exceeded normal in all three patients, reaching an average of over 350 mg. per day in the men and 240 mg. per day in the woman by the second to fourth week. Individual 24-hour specimens showed higher values. Hypercalciuria began during the second or third week after onset, and the maximal rise occurred in the third and fourth week. Hypercalciuria persisted for 6 to 10 weeks. Complete balance studies[8] showed that one man was in negative calcium balance until at least seven weeks after onset of poliomyelitis, while the woman remained in approximate balance for calcium.

B. Severe Bulbar Paralysis (Table 3, Fig. 1): This group was composed of two boys and one man. The children were critically ill and treated temporarily in respirators. The adult had extensive cranial nerve paralysis, including temporary loss of deglutition. He did not require tracheotomy or respirator. All three patients had mild associated upper-extremity and shoulder-girdle weakness, with insignificant residual paralysis. All three patients were active in bed approxi-

TABLE 2.—*Total Daily Urinary Excretion of Calcium, Phosphorus and Creatinine in Mild Bulbar Paralysis* *

	E.D., 22♀			*J.F.*, 33♂			*P.B.*, 28♂		
Wk.	Ca	P	Creat.	Ca	P	Creat.	Ca	P	Creat.
1	40	456	927	126	1,251	2,475	127	480	1,806
2	240	808	1,443	298	982	1,806	170	808	2,304
3	200	648	1,012	291	944	1,883	340	1,188	2,700
4	211	531	1,431	368	914	1,374	317	1,034	1,654
5	180	1,225	1,518	205	800	1,775	380	1,400	2,990
6	192	779	1,047	221	992	1,838	174	902	1,176
7	127	----	----	288	786	2,021	----	----	----
8	----	----	----	156	707	2,164	275	356	2,094
9	----	----	----	296	315	1,906	----	----	----

*All values expressed in milligrams per 24 hr.

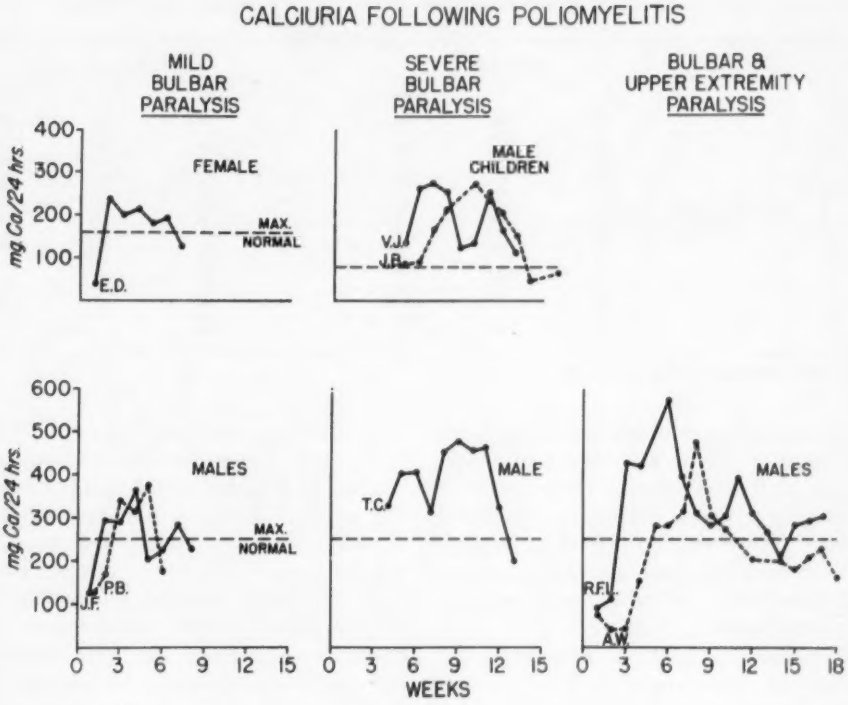

Figure 1

mately two weeks after onset of poliomyelitis and ambulated as indicated in Table 1.

Persistent hypercalciuria was seen in all three patients, although studies were started too late to observe the initial rise of calcium excretion. Hypercalciuria in the children was severe in degree, being two to three times the expected normal for this age group. The adult at least doubled his normal calcium output. Hypercalciuria persisted to the 13th week in all three patients, outlasting bedrest by several weeks.

C. Bulbar and Upper Spinal Paralysis (Table 4, Fig. 1): The two men in this group had severe paralysis of the muscles about the shoulders and upper spinal seg-

TABLE 3.—*Total Daily Urinary Excretion of Calcium, Phosphorus, and Creatinine in Severe Bulbar Paralysis* *

	T.C., 22♂			*J.B., 7♂*			*V.J., 4♂*		
Wk.	Ca	P	Creat.	Ca	P	Creat.	Ca	P	Creat.
1	----	----	----	----	----	----	----	----	----
2	----	----	----	----	----	----	----	----	----
3	----	----	----	----	----	----	----	----	----
		Admission							
4	326	1,266	1,500	----	----	----	----	----	----
					Admission			Admission	
5	402	1,269	1,423	85	299	193	138	377	352
6	405	750	1,626	89	362	346	267	624	239
7	310	432	1,026	168	378	460	271	163	320
8	451	530	----	214	439	----	256	113	261
9	479	922	2,108	----	232	----	125	323	282
10	458	712	1,606	274	328	355	133	306	294
11	462	677	2,312	237	437	352	256	376	288
12	325	769	1,673	262	388	406	169	422	----
13	200	750	1,608	152	357	440	112	443	----
14	----	----	----	44	288	470	----	----	----

*All values expressed in milligrams per 24 hr.

TABLE 4.—*Total Daily Urinary Excretion of Calcium, Phosphorus, and Creatinine in Bulbar and Upper Spinal Paralysis* *

Wk.	*A.W.*, 32♂			*R.F.*, 32♂		
	Ca.	P	Creat.	Ca.	P	Creat.
1	83	1,294	648	84	1,100	1,752
2	46	1,862	2,056	113	1,362	1,362
3	42	1,047	2,032	429	966	1,117
4	157	1,209	2,375	427	659	975
5	285	318	1,722	573	1,066	1,359
6	285	674	1,119	394	792	905
7	316	1,173	986	315	681	807
8	479	998	1,250	285	638	881
9	305	651	1,280	309	663	1,234
10	273	622	918	393	529	1,296
11	....	....	....	318	544	....
12	203	656	1,493	268	....	....
13	....	409	1,520	203	694	1,442
14	209	377	1,348	286	592	1,184
15	181	....	1,167	291	470	1,203
16	210	529	1,018	308	....	....

*All values expressed in milligrams per 24 hr.

ments in addition to diaphragmatic paralysis and lower cranial nerve involvement. Respirators and tracheotomies were required transiently to treat centrogenic respiratory failure. There was no significant involvement of back and lower spinal segments, so that active motion in bed and early mobilization was possible (Table 1).

Hypercalciuria developed at the 3d and 5th weeks and lasted until the 10th and 16th weeks, respectively. Increased urinary calcium output persisted in R. F. for weeks after he walked but ceased prior to walking in A. W. Although considerably more bone-moving muscle was denervated in these two patients, their maximal calcium excretion was comparable in degree and duration to the adult with severe bulbar paralysis.

D. Moderate Scattered Paralysis (Table 5, Fig. 2): There were three women and two men in this group. Both men and women had scattered paralyses in all four extremities and back and respiratory muscles. Some had fairly extensive bulbar involvement as well. The initial paralysis was widespread, and all patients required respirators. The intensity of paralysis was only moderate, however, so that eventually all subjects were free of respiratory aid, had good upper extremity function, and were capable of the activities of daily living. They walked with crutches, canes, or minimal bracing (Table 1).

Hypercalciuria occurred in every patient and was maximal during the fifth to the eighth week after onset (early data not

TABLE 5.—*Total Daily Urinary Excretion of Calcium, Phosphorus, and Creatinine in Moderate Scattered Paralysis* *

Wk.	*M.L.*, 28♀			*L.K.*, 22♀			*E.W.*, 28♀			*R.Ra.*, 28♂			*F.L.*, 20♂		
	Ca	P	Creat.	Ca	P	Creat.	Ca	P	Creat.	Ca	P	Creat.	Ca	P	Creat.
1	104	471	689	....	....	....	....	....	....	175	1,300	1,238	....	....	....
2	80	958	1,101	....	....	....	....	....	....	288	....	1,467	122	1,394	1,531
3	333	800	890	....	....	....	....	....	....	529	1,238	1,305	324	693	1,410
4	326	538	842	....	....	....	....	....	....	576	981	1,095	318	1,236	1,469
5	366	569	775	258	....	....	....	....	....	499	1,110	1,129	306	1,065	1,168
6	283	519	785	226	981	512	....	....	....	590	998	1,269	456	1,111	857
7	259	515	684	241	559	1,044	....	....	....	534	935	1,232	475	1,089	632
8	286	515	749	202	840	730	254	530	556	630	1,235	1,164	....	....	....
9–12†	270	547	714	188	572	800	317	608	660	384	1,018	1,182	417	405	653
13–16	220	559	645	139	464	365	266	507	621	383	697	823	378	673	707
17–20	286	....	....	115	453	748	261	586	....	....	....	....	312	674	551
21–24	....	....	....	97	418	778	....	....	....	....	....	....	132	530	441
25–28	....	....	....	108	634	755	113	....	....	....	....	....	223	504	415
29–32	....	....	....	75	482	792	....	....	....	....	....	....	295	627	905
33–36	....	....	....	....	....	....	....	....	....	....	....	....	223	643	615
37–40	....	....	....	....	....	....	....	....	....	....	....	....	211	796	644
41–44	....	....	....	....	....	....	....	....	....	....	....	....	200	894	825
45–48	....	....	....	....	....	....	....	....	....	....	....	....	227	....	....
49–52	....	....	....	....	....	....	....	....	....	....	....	....	252	....	....

*All values expressed in milligrams per 24 hr.
†All values are averaged from 4-wk. collection period.

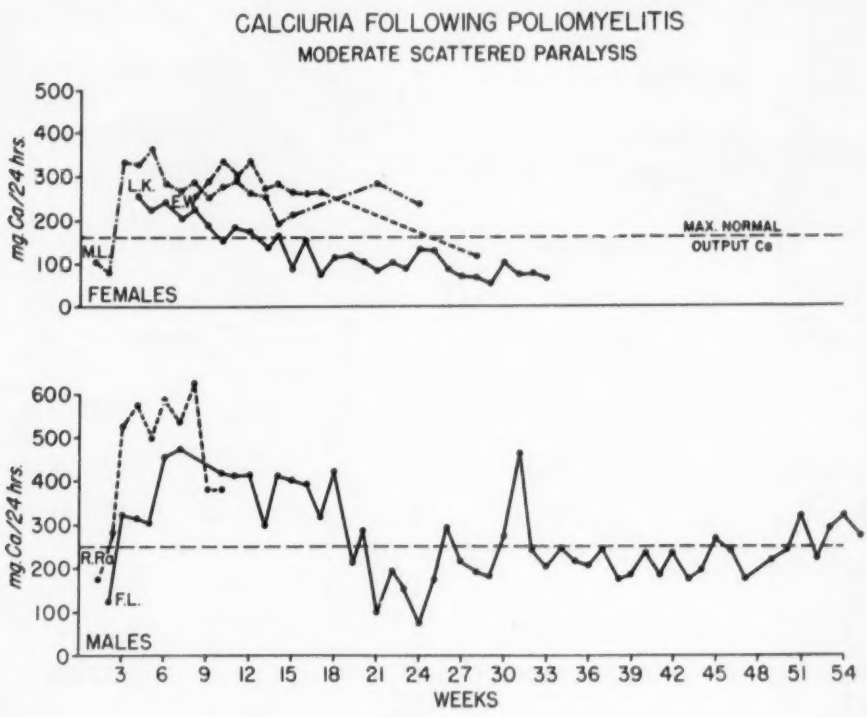

Figure 2

available on E. W. or L. K.). Calciuria returned to normal levels at 9, 21, and 26 weeks in three patients. Hypercalciuria continued beyond the study period in the other two. In F. L. and L. K. calcium excretion was normal long prior to walking. The absolute degree of hypercalciuria in the men exceeded that in the women, but daily calciuria during peak excretion periods was approximately twice normal maximal excretion in both sexes.

E. Lower Spinal Paralysis (Table 6, Fig. 3): There were three women and four men in this group. Paralysis was confined almost entirely to the trunk and lower extremities, so that each patient was paraplegic. All needed respirators transiently during acute poliomyelitis because of intercostal paralysis, but diaphragms functioned well, and independent breathing was rapidly regained. All but one patient were active in wheel chairs during convalescence, and three walked with braces (Table 1).

Hypercalciuria appeared by the fourth week when early collections were made and usually reached levels approximately twice the normal predicted output for either sex. Once it appeared, hypercalciuria persisted for months and was still present in four patients when they were discharged from the hospital on the 12th, 24th, and 40th weeks, repectively. Normal calcium excretion was reached by the 40th and 45th weeks in two men and was approached by the 40th week in another. One woman had urinary calcium excretion at normal or upper normal levels when first seen at the 13th week, and sustained elevation of calcium output was never subsequently observed.

R. H., a 17-year-old boy, had the highest urinary calcium excretion observed in any patient during this study. This lasted throughout the period of study, from the 16th to 32d weeks after his illness, despite passive standing and, later, active walking with crutches. Stool calciums averaged 575

TABLE 6.—*Total Daily Urinary Excretion of Calcium, Phosphorus, and Creatinine in Lower Spinal Paralysis**

	H.W., 36♀			*M.S.*, 33♀			*D.B.*, 28♀			*H.B.*, 36♂			*R.S.*, 34♂			*R.H.*, 16♂			*J.B.*, 28♂		
Wk.	Ca	P	Creat.	Ca	P	Creat.	Ca	P	Creat.	Ca	P	Creat.	Ca	P	Creat.	Ca	P	Creat.	Ca	P	Creat.
1	76	612	1,497	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
2	128	466	764	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	329	1,124	1,356
3	99	542	1,123	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	498	1,530	1,974
4	197	820	1,347	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	342	1,032	1,531
5	231	594	2,041	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	341	395	1,170
6	221	651	648	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	499	407	1,193
7	269	635	717	213	635	499	....	....	....	....	....	....	....	....	....	....	....	....	369	637	1,116
8	315	644	689	281	644	674	....	....	....	....	....	....	....	....	....	....	....	....	(322)	507	830
9–12†	257	580	598	316	773	716	....	....	....	....	....	....	....	....	....	....	....	....	366	631	803
13–16	245	543	1,019	227	576	445	138	268	750	....	....	....	....	....	....	....	....	....	....	....	....
17–20	266	1,315	1,058	247	484	404	148	341	627	....	....	....	....	....	....	494	705	875	....	....	....
21–24	257	479	695	263	586	519	113	311	697	....	....	....	....	....	....	736	546	819	....	....	....
25–28	....	....	....	....	....	....	117	420	640	....	....	....	....	....	....	720	790	905	....	....	....
29–32	....	....	....	....	....	....	135	516	608	....	....	....	228	584	773	749	953	883	....	....	....
33–36	....	....	....	....	....	....	129	518	525	....	....	....	136	804	901	548	887	778	....	....	....
37–40	....	....	....	....	....	....	130	686	793	....	....	....	204	868	958	506	863	904	....	....	....
41–44	....	....	....	....	....	....	....	....	....	232	942	505	292	802	813	318	380	830	....	....	....
45–48	....	....	....	....	....	....	....	....	....	248	676	834	300	783	815	....	....	....	....	....	....
49–52	....	....	....	....	....	....	....	....	....	250	773	898	249	684	827	....	....	....	....	....	....
										192	667	863	232	705	867	....	....	....	....	....	....

*All values expressed in milligrams per 24 hr.
†All values are averaged from 4-wk. collection period.

TABLE 7.—*Total Daily Urinary Excretion of Calcium, Phosphorus, and Creatinine in Diffuse Severe Paralysis*

	K.H., 16			S.W., 17			O.K., 23			R. O'C., 22			J.E., 28			R. Re., 33			D. O'C., 28		
Wk.	Ca	P	Creat.	Ca	P	Creat.	Ca	P	Creat.	Ca	P	Creat.	Ca	P	Creat.	Ca	P	Creat.	Ca	P	Creat.
1	....	....	....	....	....	....	64	348	1,483	....	....	....	....	....	....	....	....	....	....	....	....
2	186	....	....	....	....	....	230	687	1,154	....	....	....	....	....	....	....	....	....	....	....	....
3	274	....	....	....	....	....	312	708	1,174	....	....	....	....	....	....	....	....	....	....	....	....
4	201	....	....	....	....	....	323	627	855	....	....	....	....	....	....	....	....	....	....	....	....
5	221	....	....	280	....	....	298	385	1,049	....	....	....	....	....	....	....	....	....	....	....	....
6	158	....	....	....	....	....	221	550	669	....	....	....	....	....	....	....	....	....	448	840	1,425
7	....	....	....	....	....	....	256	542	603	....	....	....	....	....	....	....	....	....	328	764	899
8	....	....	....	....	....	....	282	495	709	....	....	....	....	....	....	....	....	....	353	803	1,050
9–12†	230	....	....	337	....	....	277	796	524	....	....	....	....	....	....	397	467	782	444	687	769
13–16	198	510	202	255	683	355	246	674	544	....	....	....	....	....	....	497	849	988	391	729	784
17–20	368	473	418	487	483	388	296	675	661	....	....	....	....	....	....	469	774	756	397	740	750
21–24	257	549	432	391	354	....	129	382	455	....	....	....	....	....	....	400	801	721	408	882	771
25–28	277	627	407	354	494	347	242	659	671	....	....	....	....	....	....	431	542	697	376	899	767
29–32	274	471	398	240	353	291	....	....	....	263	686	800	....	....	....	....	....	....	361	891	660
33–36	283	....	....	204	416	284	....	....	....	346	657	577	239	603	365	....	....	....	....	....	....
37–40	....	....	....	228	413	269	....	....	....	314	573	570	349	653	621	....	....	....	....	....	....
41–44	....	....	....	219	363	287	....	....	....	264	633	587	406	715	662	....	....	....	....	....	....
45–48	....	....	....	192	355	247	....	....	....	263	....	....	327	703	663	....	....	....	....	....	....
49–52	97	239	194	....	....	....	....	....	....	218	....	....	294	719	702	....	....	....	....	....	....
										264	....	....	288	666	687	....	....	....	....	....	....

*All values expressed in milligrams per 24 hr.
†All values are averaged from 4-wk. collection period.

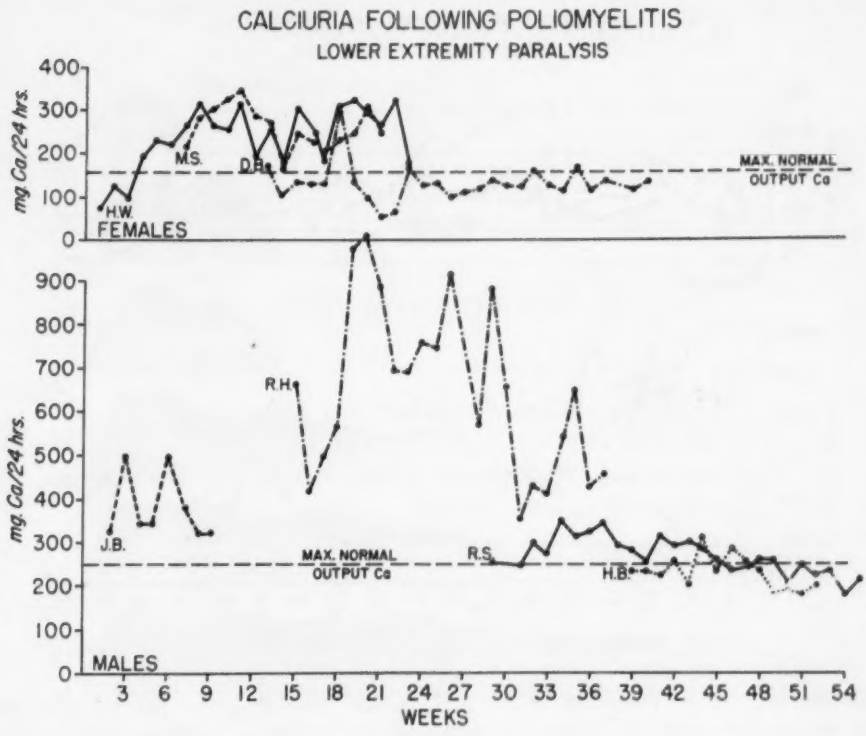

Figure 3

mg. per day. He had renal tubular dysfunction, hypercalcemia, and hypertension. The metabolic sequelae to paralysis in this boy were like those described originally in immobilized adolescent boys by Albright and co-workers.[9]

Each of the paraplegic patients with protracted hypercalciuria was standing passively long before urine calcium returned to normal. Two walked with the aid of crutches several weeks before hypercalciuria ended.

F. Diffuse Severe Paralysis (Table 7, Fig. 4): There were three females and four males in this group. All were quadriplegic. Only two were ever completely freed from artificial respiratory aid. Although they regained some function of the muscles of the upper extremities, none of these patients were mobile or capable of self-care (Table 1). Collections were begun prior to the sixth week after onset of poliomyelitis on three patients. In the four others, collections continued from the 24th to 52d weeks. When early collections were made, hypercalciuria appeared within three weeks after the onset of poliomyelitis. As in other groups, maximal hypercalciuria reached approximately twice the normal predicted output. Hypercalciuria then persisted for at least seven months and usually outlasted the study period.

Random analyses of 24-hour calcium output were made on other severely paralyzed patients 15 months or more after poliomyelitis (Tabe 8). Hypercalciuria was present only when there were demonstrable renal calculi.

Comment: Hypercalciuria was found consistently following acute paralytic poliomyelitis. Increased calcium excretion appeared in patients with mild bulbar poliomyelitis after minimal bed rest as well as in more extensively paralyzed and immobilized patients. Hypercalciuria in the early weeks

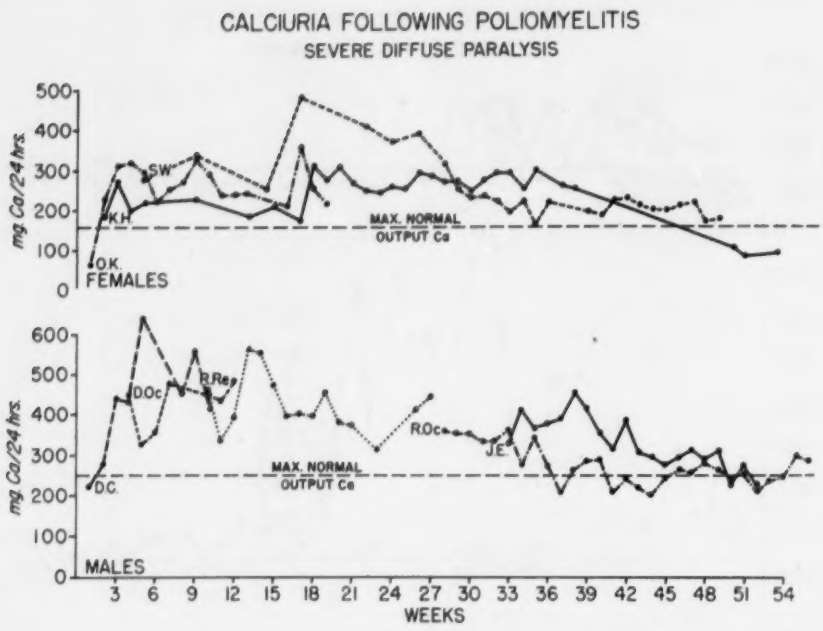

Figure 4

after illness continued unchecked despite active mobilization and the absence of any significant paralysis of bone-moving muscle. Patients with mild bulbar poliomyelitis who were fully ambulated before the end of the first week of illness had increases in calcium excretion which were only moderate. Most of the other men and women, however, excreted two to two and one-half times the normal predicted maximal daily urinary calcium within three weeks of contracting poliomyelitis (Fig. 5). Quadriplegics during the first three months excreted no more daily calcium than did some patients with high spinal or even predominantly bulbar paralysis. The initiation and intensity of daily calciuria early after poliomyelitis, therefore bore little relationship to the site and degree of paralysis.

Urinary calcium excretion reached or approached normal before or by the 14th week after onset of illness in patients with bulbar and upper-extremity paralysis. By contrast, paraplegics and quadriplegics had sustained hypercalciuria for 6 to 12 months after the onset of illness. The total duration of hyper-

TABLE 8.—*Urinary Calcium Excretion and Renal Stones in Late Convalescence*

Patient	Age, Yr.	Sex	Yr. After Onset	Ca Excretion, Mg./Day	Renal Stones
E.E.	15	F	2½	70-110	0
R.T.	28	F	3	30-64	0
P.S.	18	F	2	159	0
J.L.	32	F	3+	91	0
T.C.	33	F	10	100	0
L.B.	24	F	1¼	224	0
H.A.	47	F	1¼	159	0
F.L.	21	M	1¼	186	0
S.J.	32	F	3+	291	+
R.R.	28	M	2½	300	+
			2¾	67-127	0 (following calculectomy)
J.S.	21	M	3+	4+ Sulkowich	+
			4	36-75	0 (following nephrectomy)

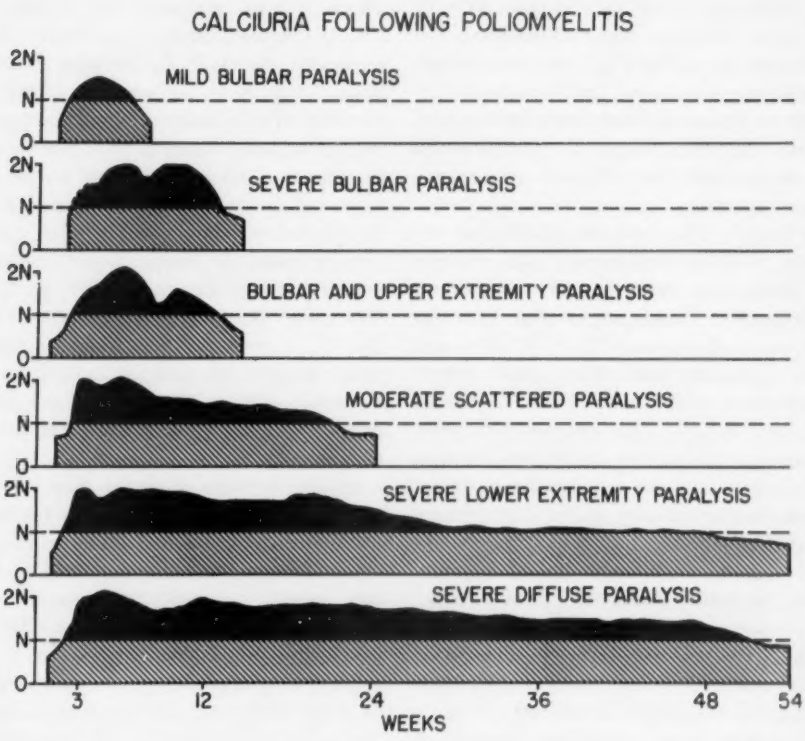

Figure 5

calciuria appeared to be directly related to the extent and degree of paralysis and the amount of immobilization resulting (Fig. 5). In some subjects, urinary calcium excretion returned to normal before walking began, while in others hypercalciuria persisted for weeks after walking started. In general, the earlier that walking started, the greater was the tendency for hypercalciuria to persist beyond the date of full ambulation.

The protracted hypercalciuria observed in this group of patients with poliomyelitis reflected profound depletion of body calcium stores. Urinary excretion in many patients exceeded the oral calcium intake of 500 mg. per day. This did not reflect a diversion of excretion routes from stool to urine, since the calcium content of random stool samples (on E. D., J. F., R. Fl, M. A., and H. W.) ranged from 300 mg. to 460 mg. daily. Whedon and Shorr's data also indicate there is no reduction in stool calcium excretion during hypercalciuria following poliomyelitis [2]; they found modest but definite increases in stool calcium during the second and third months.

II. Phosphorus Excretion.—Weekly and monthly averages of 24-hour urinary phosphorus excretion are listed in Tables 2 to 7. Patterns of phosphaturia were somewhat similar in all paralyzed groups. Some patients failed to show any great change of phosphorus excretion throughout the period of study. Many, however, had hyperphosphaturia for the first four to six weeks after onset of poliomyelitis, following which daily urine phosphorus dropped several hundred milligrams to lower levels, at which point it remained. Maximal phosphaturia was reached within the first two weeks in five of eight patients studied from onset. Phosphorus intake was not controlled, and

there were wide variations in daily urinary phosphorus excretion not paralleled by similar changes in calcium or creatinine output. No tendency was noted for phosphorus excretion to be maximal at times of maximal calciuria, nor did phosphorus excretion fall coincidently with the return of urinary calcium to normal.

Comment: The data on phosphorus excretion are in general accord with Whedon and Shorr's observation that phosphorus losses reach a maximum on the 14th day after onset of poliomyelitis.[2] Whedon and Shorr postulated that this intense hyperphosphaturia might result from dissolution of neural tissue. The intensity of phosphaturia in the present study bore no relationship to the extent of clinically estimated nervous system damage, but it is recognized that clinically evident paralysis often may be a poor index to the amount of neuronal damage in poliomyelitis.[10]

III. Serum Calcium, Phosphorus, and Alkaline Phosphatase.—These values were studied randomly on all patients after early regular analyses on a few subjects failed to show significant deviation from normal. A few serum calcium determinations were in the range of 11-13 mg. per 100 cc., but consistent elevations above normal were noted only in R. H. (Table 1). Several previous studies on immobilization and paraplegia have demonstrated that marked abnormalities in serum calcium, phosphorus, and alkaline phosphatase are rare. Deviations from the mean normal have never been statistically analyzed using a large number of observations, however.

Comment

The hypercalciuria which follows poliomyelitis or other paralytic illness outlasts by weeks or months the period of negative nitrogen balance suffered by these patients.[2,11] Mineral loss is not merely the reflection of a general catabolic reaction, therefore, and must depend on other mechanisms.

It is probable that neural factors are not directly responsible for the demineralization which follows poliomyelitis. While it is true that bone atrophy consistently follows segmental denervation, peripheral efferent neural influences appear to affect bone metabolism only indirectly by the neural control of muscle. Corbin and Hinsey noted that there is no evidence that motor nerve fibers terminate directly in bone.[12] Locally denervated extremities demineralize no more rapidly than do those placed in casts[13] (muscle atrophies as rapidly with total disuse as it does following efferent denervation[14]). The x-ray appearance of bone of involved limbs late in the course of muscular dystrophy differs in no way from the appearance of extremities late after denervation atrophy.[15]

It also appears doubtful that peripheral autonomic neural changes are responsible for inducing demineralization after poliomyelitis. The sympathetic control of vascular supply can sometimes modify bone growth and calcification, but the effects are not always predictable.[16-18] Harris'[19] statement that sympathectomy increases the rate of growth of bones in denervated extremities after poliomyelitis is unconfirmed. Corbin and Hinsey[12] demonstrated that experimental deafferentation and sympathectomy have no influence on x-ray appearance or weight of extremity bones. Sympathetic changes in poliomyelitis are not prominent early in the illness[20] when hypercalciuria begins. Peripheral autonomic abnormalities also bear little relationship to the site of skeletal muscle paralysis,[21] and they have never been demonstrated to be quantitatively related to the decalcification. Finally, autonomic abnormalities are usually long-lasting after poliomyelitis, while hypercalciuria is more limited in time.

Perhaps the theory most widely advanced is that the demineralization which follows paralysis results from a loss of mechanical stresses and strains on bone consequent to immobilization.[22,23] It has been reasoned that muscular and postural forces are necessary to maintain the normal balance between production and destruction of calcified osteoid; interruption of these forces permits

osteoclasis to proceed unabated, while osteoplasis ceases for want of physical stimulation. Observations which appear to support the theory that the mechanical effects of immobilization are primarily responsible for the demineralization which follows paralysis are several: Whenever mechanical forces are interrupted by prolonged severe immobilization, osteoporosis occurs [23]; conversely, immobilization is common to demineralized states other than paralysis, such as fractures [24] or even artificial casting of the body in plaster.

Several things suggest, however, that more than the interruption of physical forces on bone must be involved in producing hypercalciuria and osteoporosis after poliomyelitis or, for that matter, after other nervous system injuries. After poliomyelitis, hypercalciuria climbs to approximately two to two and one-half the normal maximal output and then levels off. This reponse sometimes does not reach maximum for up to seven weeks after illness. The magnitude of the initial rise in calcium excretion is not proportional to the degree of paralysis or immobilization, and seldom does daily urinary calcium loss exceed 500-600 mg. Analysis of the studies of other investigators on patients with poliomyelitis,[2] paraplegia,[1,25] and fractures or osteotomies [24] reveals that the intensity of early hypercalciuria was approximately the same as was found in the patients with poliomyelitis studied in this laboratory. Within each study and from study to study, however, there were wide variations in the amount of the body immobilized. The quantitative interruption of "stress and strain" was, accordingly, far from constant. Differences in calcium intake had surprisingly little effect on the constancy of the hyperexcretion.[24,26] The response did not vary with the type of trauma, but usually it was quantitatively greater in the clinical studies than when immobilization was induced in healthy subjects.[23]

If pure mechanical effects are responsible for hypercalciuria, it is surprising that the response sometimes is delayed up to seven weeks after immobilization. Mechanical factors would not appear to explain the hypercalciuria observed in mild bulbar poliomyelitis, since these patients were not immobilized. Another observation against the theory that hypercalciuria results solely from interruption of mechanical stresses and strains on bone is the ineffectiveness of tilting: Passive standing and tilting increase mechanical forces on bone but fail to modify hypercalciuria in patients with either poliomyelitis [27] or paraplegia.[28] Indeed, our own data indicate that after poliomyelitis, increased activity at times appears to increase rather than to decrease excessive urinary calcium excretion. This is in contrast to the effect of passive mobilization on casted healthy volunteers on whom the slow oscillating bed reverses or prevents demineralization.[29] Despite a general correlation between the degree of paralysis and immobilization and the duration of hypercalciuria in the present study, there was also evidence that more than mechanical stresses and strains were required to reverse the drain on mineral stores. Hypercalciuria ceased in some subjects before they walked, while in others hyperexcretion long outlasted ambulation. A similar phenomenon was observed by Howard in fracture patients.[24]

Since neither direct peripheral neural influences nor the effect of interruption of physical forces on bones adequately or totally explain the demineralization which follows poliomyelitis, other factors must be sought. Hypercalciuria does not follow other systemic non-nervous-system illnesses comparable in severity to mild bulbar poliomyelitis.[30] This suggests that either central nervous system involvement is a factor in inducing mineral loss in poliomyelitis or that the illness sets in motion more intense catabolic reactions in non-neural tissue than would be expected from its clinical severity. Indication that the nervous system may be important in the production of decalcification is also found in tuberculosis; with non-osseous disease, renal stones develop commonly only in patients with meningeal and central nervous system involvement.[31]

Our evidence is insufficient at this point to identify specific neurohumoral mechanisms which may cause excessive wastage of calcium in neurologic disease. Adrenal pathways may be involved eventually, since elevated 17-ketosteroids have been found in some patients with paralytic poliomyelitis,[32] particularly in young adults with hypercalcemia and markedly elevated urinary calcium. A single patient in the present series (R. Fl., Table 1) had markedly elevated urinary 11-oxysteroids at the time when his calcium excretion was maximal. Attempts to assess the significance of brain stem autonomic lesions in the genesis of these abnormal metabolic responses are in progress.

Summary

Urinary calcium, phosphorus, and creatinine excretion were studied serially after paralytic poliomyelitis in 27 adults and children for periods lasting 2 to 12 months. Less detailed observations were made on 27 additional patients. The patients had paralysis which ranged from mild cranial nerve involvement to total quadriplegia. The degree of immobilization ranged from practically none to severe.

All patients studied immediately subsequent to acute illness had a significant increase in urinary calcium excretion, which reached a maximum in the second to eighth weeks after poliomyelitis. This early hypercalciuria attained levels which averaged twice the predicted normal urinary excretion for age and sex. The rise was independent of the site or degree of paralysis or immobilization.

Hypercalciuria ceased by the 14th week after onset of poliomyelitis in patients with bulbar and high spinal paralysis, whereas it continued up to 12 or more months in severely paralyzed persons. Only two patients had excessive calcium excretion lasting more than 15 months after onset of poliomyelitis. Both had renal calculi.

The evidence suggests that demineralization after poliomyelitis is initiated and maintained by systemic neurohumoral factors as yet only partially clarified. These factors appear at least to supplement any loss of stress and strain on bones resulting from immobilization.

The late Dr. Ephraim Shorr and Dr. G. Donald Whedon stimulated and criticised much of this work. Technical assistance was provided by Ruth Uchida, Molly Tsalaky, and Herta Dumpis.

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Antiemetic Properties of a New Chlorphenothiazine Derivative, Proclorperazine

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Nausea and vomiting, among the most distressing symptoms the patient may have to endure, may at the same time seriously interfere with his proper management. Considerable evidence indicates that there are two components to the central nervous system physiology of this symptom complex. First, emetic substances introduced into the body and circulating in the blood may cause nausea and vomiting either by activating the chemoreceptor trigger zone in the floor of the fourth ventricle or by acting directly on the nearby emetic center. Second, abnormal labyrinth or extracranial activity may set up nerve reflexes which activate the emetic center.[1] The control of nausea and vomiting, therefore, depends ultimately on suppression of activity of the emetic center or of the chemoreceptor trigger zone.

Chlorpromazine, a widely used and potent antiemetic of the phenothiazine series, exerts a minor depressant action on the emetic center.[2] It also provides an excellent means for blocking or depressing the chemoreceptor trigger area.[3,4] While chlorpromazine is highly effective against nausea and vomiting of many etiologies, it exerts much less action against these symptoms when they result from motion sickness.[5]

Sedation, scopolamine (hyoscine), and certain antihistaminics also help suppress nausea and vomiting but are mostly used for the suppression of nausea and vomiting from motion sickness.

Of the antihistaminics, diphenhydramine (Benadryl); the phenothiazines, promethazine (Phenergan) and ethopropazine (Parsidol), and, more recently, cyclizine (Marezine), chlorcyclizine (Perazil) and meclizine (Bonamine), antihistaminics of the piperazine series, have gained much favor as useful agents in combating motion sickness.[6] These agents possibly combine sedation with some inhibition of the emetic or chemoreceptor trigger area; their exact mode of action is not known.

A combination of the structural characteristics that appear optimum for activity in the phenothiazine and the piperazine series of drugs might be expected to result in an agent with antiemetic activity. Such a preparation is provided by proclorperazine. This substance, a new chlorpromazine congener, has become available for the treatment of mild mental and emotional disturbances and nausea and vomiting of various etiologies. Its formula is shown in the Figure. It can be seen that it combines structural features of chlorpromazine and cyclizine, each of which is a highly effective inhibitors of nausea and vomiting. The high order of antiemetic activity actually found with proclorperazine was most gratifying.

Pharmacology

Acute toxicity studies in mice showed the L. $D._{50}$ oral dose of proclorperazine to be 2050 mg/kilogram in four days, comparing favorably with chlorpromazine, whose L. $D._{50}$ oral dose is 335 mg/kilogram in 14 days. In chronic toxicity studies on rats given 50 mg/kilogram for one month there

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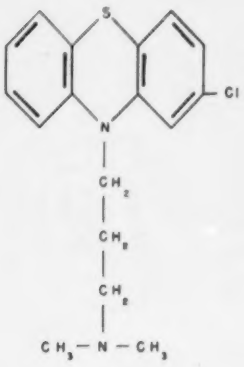
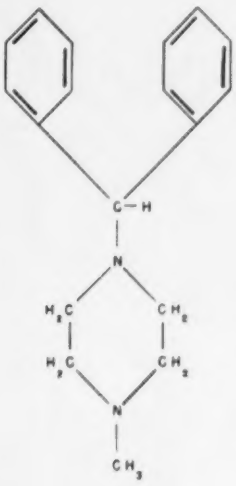
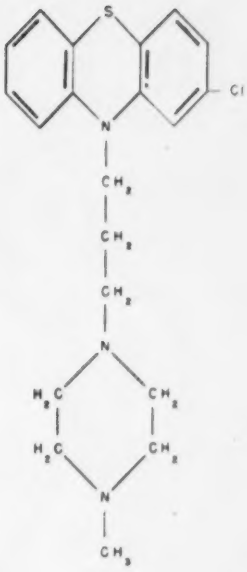


Chlorpromazine



Cyclizine



Proclorperazine

was no interference with growth, weight, behavior, or hematopoiesis. Histological examination showed no toxic lesions of the kidney, liver, lungs, or spleen. Dogs given 30 mg/kilogram for one month showed slight weight loss, but there was no interference with behavior, and histological examination of organs was normal. There was no interference with kidney or liver function. In suppressing apomorphine-induced vomiting in dogs, proclorperazine was found to be superior to chlorpromazine. A dose of 0.35 mg/kilogram (compared with a dose of 2.1 mg/kilogram of chlorpromazine) reduced by 50% the emesis caused by subcutaneous injection of 0.1 mg/kilogram of apomorphine. In potentiating hypnotics, analgesics, and general anesthetics, it is less active than chlorpromazine. In mice proclorperazine has only about two-thirds the potency of chlorpromazine in depressing motor activity. In dogs it exerts about one-half the hypotensive and sympathetic depressant action of chlorpromazine. The drug is approximately 1.6 times more potent than chlorpromazine in blocking conditioned reflexes in rats.[7]

Methods

Tablets of 5 mg., ampules containing 10 mg. of the drug in 1 cc., and 50 mg. rectal suppositories were used to study the control proclorperazine exerts on nausea and vomiting of various etiologies, hiccough, and vertigo.* The Table summarizes the results of our observations of 25 cases. Whenever possible, proclorperazine was compared with chlorpromazine. The drug was well tolerated by the oral, intramuscular, and rectal routes.

Conclusions

Proclorperazine exerts an antiemetic effect in smaller doses than chlorpromazine. It suppresses nausea and vomiting at only slightly more than half the usual dose required with chlorpromazine. In six patients it was more effective than chlorpromazine.

Vertigo in two patients with Ménière's syndrome and hiccough in one patient with uremia and in one following gastrectomy were controlled.

Slight drowsiness was a common but usually desirable side-effect. At dosages

* Proclorperazine was supplied as Compazine by Smith, Kline & French Laboratories, Philadelphia.

Effect of Proclorperazine on Nausea and Vomiting

Patient	Diagnosis	Nausea and Vomiting		Daily Dosage, Mg.*	Response†	Side-Effects	Remarks
		Severity	Duration				
A.B.	Chronic hepatitis	Moderate	20 days	100	Excellent	Extreme drowsiness	Felt "drugged"
M.D.	Infectious mononucleosis	Moderate	3 days	40	Good	Drowsiness	Hepatitis complicated by mononucleosis
D.N.	Pregnancy, 11 wk.	Mild	6 wk.	40	Good	Lethargy, dizziness	Fainted for the first time in her life, although no hypotension detected
M.S.	Uremia	Moderate	14 days	40	Good	None	
S.M.	Pregnancy	Moderate	1 wk.	80	Good	Drowsiness	
S.H.	Carcinoma of the liver	Moderate	1 wk.	50	Good	Drowsiness	Very slight improvement, terminal illness
P.P.	Uremia	Moderate	1 wk.	100	Excellent	Drowsiness	
M.L.	Esophageal diverticulum excised	Moderate	4 days	40	Good	Drowsiness	Not disturbing
W.C.	Crush syndrome	Severe	3 days	50	Poor	Drowsiness, lethargy	Chlorpromazine subsequently controlled nausea and vomiting
C.B.	Severe status asthmaticus and acute anxiety	Mild	1 day	50	Good	1 hr. episode of aphasia 20 min. after drug	Patient very high strung and nervous, question value of drug here
A.A.	Disseminated lupus erythematosus	Severe	5 days	50	Excellent	Drowsiness	Numbness in mouth; questionable side-effect
H.T.	Carcinomatosis	Severe	1 day	50	Excellent	Drowsiness	
M.P.	Metromenorrhagia; iron-deficiency anemia	Moderate	1 wk.	80	Excellent	None	Intravenous iron therapy was probable cause of nausea and vomiting
W.R.	Cor pulmonale	Moderate	2 wk.	80	Excellent	Severe drowsiness, lethargy	Patient had low-sodium syndrome complicating the picture
N.W.	Common-duct obstruction by carcinoma of pancreas	Moderate	4 days	50	Excellent	Drowsiness	Much better result than with chlorpromazine, 25 mg. 4 times a day
R.M.	Chronic glomerulonephritis, uremia	Severe	2 wk.	200	Poor	Drowsiness	Chlorpromazine, 25 mg. 4 times a day, used concomitantly without benefit
C.S.	Hypertensive encephalopathy	Severe	1 wk.	80	Good	Restlessness, agitation	Chlorpromazine, 25 mg. 3 times a day, did not control nausea and vomiting
A.P.	Chronic pyelonephritis and terminal uremia	Severe	1 mo.	40	Good	None	
E.M.	Acute pyelonephritis	Severe	1 wk.	120	Excellent	Drowsiness	Chlorpromazine, up to 50 mg. I.M. 3 times a day, had failed completely
C.A.	Uremia with hiccoughs for 2 days	Moderate	2 wk.	40	Excellent	None	Hiccoughs relieved promptly
M.A.	Postoperative gastrectomy for duodenal ulcer with hiccoughs	Moderate	2 days	40	Excellent	None	Hiccoughs relieved promptly
A.W.	Ménière's syndrome	Severe	2-3 wk.	100	Excellent	Felt "peculiar" on 100 mg.	Felt "out of this world" on 100 mg. a day
R.H.	Postoperative diabetes	Mild to severe	4 days	50	Excellent	Drowsiness	Chlorpromazine, 25 to 50 mg. 4 times a day, had not controlled nausea and vomiting for 4 days
H.P.	Chronic pyelonephritis, uremia	Moderate	Sporadically for 1 yr.	40	Good	Moderately drowsy	
D.S.	Ménière's syndrome	Moderate	1 yr.	40	Excellent	None	Chlorpromazine, 25 mg. 4 times a day, failed to control nausea and vomiting
B.H.	Ménière's syndrome			40	Excellent	None	Patient had no nausea and vomiting but severe vertigo, which responded promptly

*Maximum amount given any one day.
†Excellent indicates complete control of nausea and vomiting; good ,vomiting controlled and much of the nausea; poor, little or no effect on the nausea or vomiting.

higher than 60 mg. a day proclorperazine may yield untoward effects: occasional confusion, dizziness, or fainting. One patient complained of mild gastric irritation after each dose of the drug; this appeared after she had been taking 60 mg. of the drug daily for three weeks. Although no jaundice or other serious toxic effects were observed in this study, a much larger series of patients must be followed before any satisfactory opinion can be reached in this respect. Since the drug is effective in smaller doses than chlorpromazine, the organism is exposed to less of it, which may in turn lead to less possibility of toxic reactions developing.

On the basis of our experience proclorperazine is an effective antiemetic agent when given in doses of 10 mg. every four or six hours. The drug deserves further study in patients with nausea, vomiting, hiccoughs, and vertigo and in many more persons before its exact role in therapy can be determined.

Summary

A new antiemetic agent—proclorperazine—is described.

It proved effective in 25 cases of nausea and vomiting of various etiologies in a dose of 10 mg. by mouth or intramuscularly every four to six hours or a rectal suppository of 50 mg. once daily.

In two patients with Ménière's syndrome with severe vertigo it effectively relieved the dizziness.

On long-continued therapy mild gastric irritation may occasionally occur, and in higher doses it can cause confusion, dizziness, and fainting.

No jaundice, agranulocytosis, or other serious toxic effects were observed.

Since it is effective in smaller doses than chlorpromazine, there is a good possibility that it will actually produce fewer toxic side-effects.

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Cryptococcal Infection Treated with 2-Hydroxystilbamidine in a Patient with Boeck's Sarcoid

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Cryptococcal infections (Torula) in man are uncommon, most cases having appeared in the literature as individual reports. The disease does not appear to be endemic, having a generalized distribution throughout the world. The majority of cases in the literature have been of the meningeal form; however, a few reports have presented only pulmonary, cutaneous, or osseous involvement. A variety of therapeutic agents have been employed with generally disappointing results. Evaluation of therapy has been made difficult because of scattered, individual case reports as well as spontaneous remissions seen in this disease. We therefore urge the report of all such cases and present one of our own. In presenting this case we have two considerations; therapy with 2-hydroxystilbamidine and the significance of a coexisting granulomatous process.

Report of a Case

History.—This 27-year-old Negro male veteran was apparently well until November, 1952, when he was hospitalized in Japan for the treatment of thrombosed hemorrhoids. While there, a routine chest film revealed infiltrative nodular lesions in the right lung field. A thorough examination revealed no evidence for tuberculosis. He was then returned to active duty in Korea. In February, 1955, he was discharged. He then attended school and worked as a laborer, at times being forced to change jobs, frequently because of "a spot in the right lung" seen in routine x-rays.

In November, 1953, the patient developed an aching pain in the right anterior chest which was intermittent, nonradiating, and unrelated to cough or deep inspiration. He denied any other respiratory tract symptoms. In January, 1954, this chest pain became continuous and radiated to the back along the rib margin at the third and fourth dorsal levels.

In May, 1954, the patient was admitted to a VA Tuberculosis Hospital. At that time an ovoid mass was found in the right subscapular area which had been present several days before admission. The mass was described as being 5×3×3 cm. in size, freely movable, firm, and nontender. An x-ray of the chest wall revealed a soft-tissue mass without calcification or erosion of the ribs. The chest film revealed soft, nodular infiltrations in the right first, second, third, and fourth interspaces, with some confluent infiltrations in the second interspace, and was interpreted as moderately advanced tuberculosis. Six smears and cultures of gastric washings for A. F. B. (acid-fast bacilli) and three for fungi were negative. First and second strength P. P. D. skin tests were negative, Coccidioidin (1:100) and histoplasmin (1:100) skin tests were also negative. Routine urinalysis showed many WBC's and an occasional RBC. A C. B. C. was within normal limits. Blood serological tests for syphilis and complement fixation tests for histoplasmosis, blastomycosis, and coccidioidomycosis were all negative.

In June, 1954, the patient was transferred to the Chest Service of another VA Hospital. Additional physical findings at this time were enlarged submandibular nodes, a large node in the right supraclavicular area, and discrete firm glands in the axillary, inguinal, and epitrochlear areas. Laboratory data at this time were as follows: A sputum culture for predominant organisms revealed pneumococci. Tuberculin skin tests, as well as those for fungi, were again negative. The serum albumin was 4.25, and globulin, 3.6 gm. Thymol turbidity was 7.1 units. Urinalysis revealed 4-5 WBC per high-power field. Two cultures of an excised cervical node were negative for A. F. B. An ECG was within normal limits. Pulmonary function tests were all within normal limits. A posteroanterior and right lateral view of the chest revealed diffuse minimal fibrotic changes throughout both lungs with moderately heavy fibrotic changes in the right upper lobe, inter-

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From the Veterans Administration Hospital.

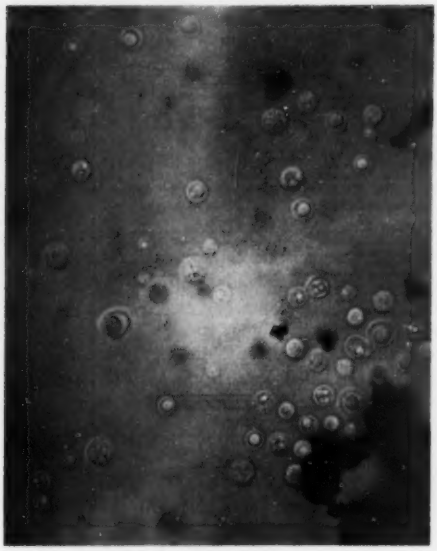


Fig. 1.—Encapsulated forms of Cryptococcus neoformans growing out in culture from material obtained from the chest wall abscess.

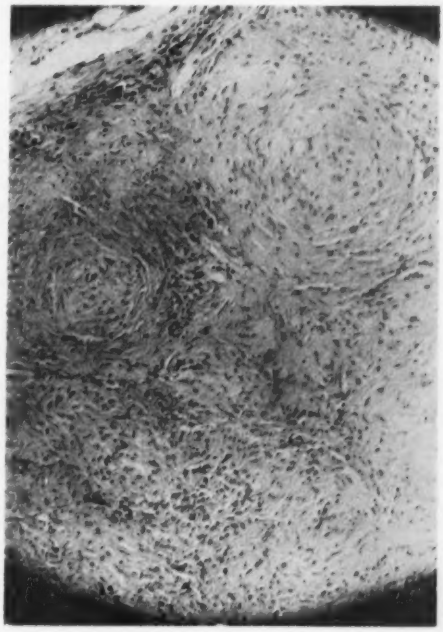
preted as sarcoidosis or old arrested tuberculosis. X-rays of both hands and feet were negative. A biopsy of the right supraclavicular fat pad was reported as a tuberculoid inflammatory reaction (Fig. 2). A bronchoscopy was negative. The patient was discharged July 16, 1954, with a diagnosis of sarcoidosis.

The patient remained asymptomatic until August, 1954, when there was a return of aching right chest pain radiating to the back. The mass on the right lateral chest wall had increased to the size of a baseball. Because of this and aching pain in the right flank, at times radiating to the groin, he was admitted to the Veterans Administration Hospital at Hines, Ill., on Oct. 12, 1954. At this time the patient denied additional respiratory and urinary tract symptoms. The past history was noncontributory.

Physical Examination.—Physical examination revealed a well-developed, poorly nourished Negro man, who appeared chronically ill. His temperature was 99.6 F; pulse, 88, and blood pressure, 110/80. There were discrete, nontender nodes in the posterior cervical chains bilaterally. There was also a large node in the left supraclavicular area which was slightly tender and firm. There was a nontender, fluctuant 10×8 cm. mass in the right subscapular region. The abdomen was scaphoid. There was a slightly tender 2×3 cm. subcutaneous nodule in the right flank. Definite tenderness was elicited on palpation of the right costovertebral angle. On deep inspiration a tender mass was palpated in the right lumbar region which appeared to be the lower pole of the right kidney. The left kidney, the liver, and the spleen were not palpated. In addition to those lymph nodes described above, there were firm, discrete nodes in the left axillary region and bilaterally in the epitrochlear, inguinal, and femoral regions. The remainder of the physical examination was noncontributory.

Laboratory Data.—The urinalysis revealed a specific gravity of 1.020, a faint trace of albumin, and 10 white cells and occasional red cells per high-power field. The red blood cell count was 4.96, with 13.5 gm. of hemoglobin. A peripheral smear revealed moderate targeting of the erythrocytes; however, the paper electrophoretic pattern was typical of normal adult hemoglobin. A blood serology test for syphilis was negative. Culture of urine from both the right and the left ureters was nonrevealing. Urines through Jan. 3, 1955, contained white cells and traces of albumin, but results became negative after Jan. 24, 1955. The total serum protein was 7.7 gm.; albumin, 4.4 gm., and globulin, 3.3 gm. A fasting blood sugar, P. S. P., N. P. N., and urea clearance were all normal.

Fig. 2.—Photomicrograph of a section of a supraclavicular lymph node with tubercle formation, epithelioid cells, and lymphocytes, surrounded by hyalinization with absence of central necrosis.



Urine cultures for A. F. B., as well as findings in two guinea pigs inoculated with urine from both ureters, were negative. Smears and cultures from purulent secretions of the right subscapular abscess, tissue of the subcutaneous nodule of the right flank, and bone marrow were negative for A. F. B., as were findings in two guinea pigs inoculated with secretions from the abscess and tissue from the subcutaneous nodule. Bone-marrow aspiration, spinal fluid, urine, and two gastric washings were negative for fungi. Cultures for yeast and fungi on material from the right subscapular abscess and right flank nodule secured on Oct. 15, 1954, grew out Cryptococcus neoformans (Torula organism) (Fig. 1). After intraperitoneal mouse inoculation with culture material, autopsy revealed encapsulated yeast cells in the brain, and the brain culture was positive for C. neoformans. A spinal tap revealed normal pressure dynamics, and examination of the spinal fluid revealed 1 lymphocyte, 42 mg/100 cc. sugar, 695 mg. chloride, 28 mg. protein, and negative globulin and serologic test for syphilis. P. P. D. No. 1 (dilution 1:1000), P. P. D. No. 2 (dilution 1:250) and old tuberculin (dilution 1:10) skin tests were all negative. Skin tests for fungi were also negative.

A chest film on admission showed an area of nodular infiltration in the right second and third interspaces. No calcifications were visible. There was a moderately enlarged right hilar node. Rib detail, x-rays of the dorsal and lumbosacral spines, and an intravenous pyelogram were negative. A retrograde pyelogram revealed a normal kidney outline on the left. On the right, the calyces were slightly blunted, especially the upper calyces, which was consistent with tuberculosis. A barium enema was negative. The skull and a long-bone survey were negative except for the finding of a rounded area of decreased density about 1 cm. in diameter in the distal third of the right femur. A sternal marrow aspiration was slightly hypocellular and fibrotic, but organisms were not seen. Review of the right supraclavicular node biopsy done elsewhere suggested Boeck's sarcoid or hyperplastic tuberculosis. Biopsy of the subcutaneous nodule of the right flank revealed subacute inflammation. No organisms were seen in either biopsy. Biopsy of the nodule at the site of injection of Kveim material was interpreted as an epithelioid reaction. Sensitivity tests on culture material revealed no inhibition of growth at 500γ per milliliter of sulfadiazine or stilbamidine; 2-hydroxystilbamidine and aminostilbamidine caused no inhibition at 100γ per milliliter, but complete inhibition at 250γ. Propamidine showed no inhibition at 25γ per milliliter but complete inhibition occurred at 50γ per milliliter for three days.

Hospital Course.—Eight days after admission, on the assumption that the patient had generalized tuberculosis, he was given 1 gm. of streptomycin twice a week and 12 gm. of aminosalicylic acid a day. On Nov. 10, 1954, a culture revealed a growing fungus, the identity of which could not be determined. On Nov. 18, 1954, it was felt that the organism was C. neoformans, and mouse inoculations were started. At this time sulfadiazine, 1 gm. every six hours, was added to the regimen, being increased to every four hours on Nov. 29, 1954. The node in the left supraclavicular area was now larger. On Nov. 3, 1954, after seven weeks of therapy, streptomycin and aminosalicylic acid were stopped. The patient had gained 6 lb. of weight but still ran an intermittent febrile course. On Dec. 2, 1954, autopsy of the mouse which had been given inoculations demonstrated Cryptococcus organisms in the brain. On Dec. 6, 1954, it was decided to stop therapy with sulfadiazine, which he had received for two weeks, and commence giving 2-hydroxystilbamidine, 150 mg. in 200 cc. of isotonic saline intravenously daily. A culture from material taken before 2-hydroxystilbamidine had been started was negative; but another done after 3.15 gm. of 2-hydroxystilbamidine had been given grew Cryptococci. Eight weeks after 2-hydroxystilbamidine therapy had been started, the patient became afebrile. The right subscapular abscess was completely aspirated on Dec. 27, 1954, and was apparently healed by Jan. 13, 1955, six weeks after 2-hydroxystilbamidine therapy had been started. The left supraclavicular node, which had become fluctuant, was also decreasing in size. Therapy was completed on Feb. 15, 1955, when a total of 10.04 gm. of 2-hydroxystilbamidine had been administered. He had gained 9 lb. in weight and was asymptomatic. A review of chest films taken at intervals showed no change in the lesion. There was no further right flank pain, and the right kidney seemed smaller on palpation and was nontender. The patient was discharged on March 3, 1955.

On recall, one month later, he was still asymptomatic. The fluctuant node, which had been in the left supraclavicular region, could not be palpated. The urine was negative, and the chest film, as well as an x-ray of the right femur, revealed no change.

Four months after therapy had been completed, the patient was readmitted to the hospital because of progressive involvement of the

reticuloendothelial system. Since the last visit, in April, 1955, he had been working in an animal-hide warehouse. The history and systemic review was nonrevealing.

On physical examination, done on July 6, 1955, there was noted to be a vesicular eruption confined to the bearded area of the face. The spleen was found to be palpated 3 cm. below the left costal margin, in the left midclavicular line. The liver and kidneys were not palpated at this time. There was a generalized lymphadenopathy consisting of firm, discrete nodes as large as 2 cm. in diameter in some areas. The rest of the physical examination was essentially negative.

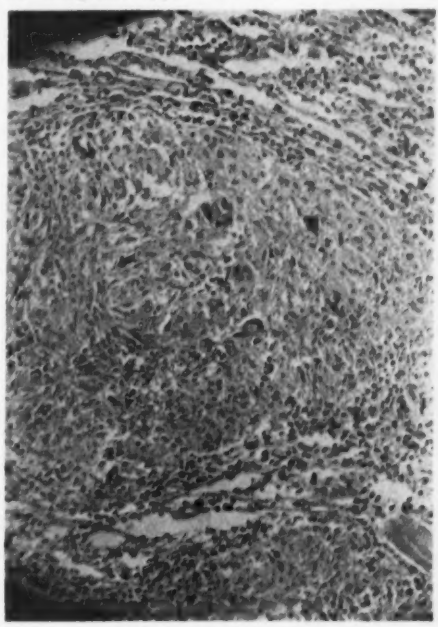
On admission the urine contained a trace of albumin, 8 white blood cells and 5 red blood cells per high-power field, and few bacteria. A repeat urine contained a few white blood cells. The red cell count on admission was within normal limits, but the total white cell count was 3400, with a normal differential count. Additional white cell counts were never higher than 5000. An N. P. N. and fasting blood sugar were normal. Thymol turbidity was 5 units; A/G, 4/3.2; alkaline phosphatase, 8.4 Bodansky units, and the van den Bergh, 0.2 mg. direct and 0.5 mg. indirect. A P. S. P. was normal. Heterophile and Brucella agglutinations were negative. Tuberculin skin tests as well as those for fungi were negative. Repeated smears and cultures of sputum, as well as urine specimens on cystoscopy, were negative for A. F. B. and fungi. On one occasion Candida albicans grew out on a sputum culture. A review of the patient's chest x-ray since October, 1954, including a chest laminogram done on Nov. 4, 1954, revealed that the infiltration in the right upper lobe appeared to have remained static but there had been a gradually increasing nodular and streaky infiltration in the upper half of the left lung and the lower lobes of both lungs. Body-section roentgenography failed to show any evidence of cavitation or calcification.

Pulmonary function studies were repeated and were within range of normal. The lesion of the right femur had not changed since Dec. 3, 1954. An intravenous pyelogram showed slight blunting of the superior calyx on the right, consistent with pyelonephritis. The left ureter was deviated medially as it passed over the psoas shadow. However, a retrograde pyelogram revealed no abnormalities of the ureter. The bone marrow was compatible with chronic tissue breakdown. A smear and culture of one of the vesicular lesions of the face was negative for fungi, but a biopsy demonstrated molluscum contagiosum. On July 8, 1955, a left epitrochlear lymph node biopsy was read as compatible with Boeck's sarcoid. A section stained with periodic acid Schiff stain did not reveal any organisms.

Because of the possibility of widespread dissemination of cryptococcosis with involvement of the spleen, a splenectomy was done on Aug. 16, 1955. At surgery the liver was found to be studded with multiple plaque-like, greenish areas, measuring 1 cm. in diameter. The spleen was approximately three times normal size, weighing 150 gm., and contained lesions similar to those found in the liver. The microscopic section showed almost complete replacement of normal splenic architecture by rather large tubercle formations. In a very few of the large tubercles there was some suggestion of caseation within the center (Fig. 3). The section was searched for bacteria and parasites, and none were found. Smears and culture of splenic material for A. F. B. and fungi were negative. The pathologist's impression was that of Boeck's sarcoid or hyperplastic tuberculosis.

Immediately postoperatively the patient ran a febrile course with a neutrophilic leukocytosis and complained of right infrascapular pleuritic pain, but the chest plate did not reveal any change. The patient responded to Combiotic

Fig. 3.—Section of splenic tissue, showing tubercles with epithelial cells and giant cells of the Langhans type.



(penicillin and dihydrostreptomycin) and on Sept. 23, 1955, was discharged.

He was seen on follow-up examination on Nov. 4, 1955, eight months after his initial admission to our hospital. The patient had no complaints except for occasional right chest pain. His weight had remained static. On physical examination there was marked improvement of the vesicular eruption of the face. There was still a generalized adenopathy, and there were now 4 cm. enlarged, bilateral femoral nodes. The abdominal incision was well healed. The liver and kidneys were not palpable. A routine urinalysis and C. B. C. were normal.

On May 2, 1956, fifteen and one-half months after therapy with 2-hydroxystilbamidine had been completed, the patient was seen for the last time before this writing. The patient's only complaint was that of vague, intermittent chest pain. The physical examination was essentially negative except for adenopathy. There were several 1 to 1.5 cm. nodes in the right cervical region, 1.5 cm. nodes in the left posterior cervical chain, and 1 to 4 cm. nodes bilaterally in the axillary, epitrochlear, inguinal, and femoral regions.

Routine urinalysis revealed a few red and white blood cells. A complete blood cell count was normal. Liver function tests were within normal limits except for an alkaline phosphatase of 8.2 Bodansky units and an A/G ratio of 4.2/3.6. Pulmonary function studies revealed no change since Sept. 15, 1955. An x-ray of the chest showed no significant change since Nov. 4, 1955. The intravenous pyelogram revealed no abnormalities. The N. P. N. was 25.2. A liver biopsy was reported as demonstrating normal architecture of the liver. Cultures for fungi on material from the liver biopsy and a left cervical node were negative. Smears and cultures for A. F. B. as well as guinea-pig inoculation of material from these tissues were also negative. A 24-hour urine culture for A. F. B. was negative. The patient's hospital course was uneventful.

Comment

Therapy in cryptococcosis has not only been disappointing but is difficult to evaluate. Aside from scattered cases with conflicting results, spontaneous remissions make any evaluation of a case as a complete cure hazardous. Fisher states that the infection may run a chronic course with natural remissions, at times lasting for many months.[1] Willard and Wolff reported a case of cryptococcal menigoencephalitis with a spontaneous remission and felt that such a remission in any case of meningoencephalitis should strongly suggest the occurrence of torulosis (cryptococcosis).[2]

Therapy of this disease has been variable. Conant et al. reported encouraging results in cutaneous cryptococcosis by the use of excision and drainage followed by local x-ray treatment and iodides by mouth. They also had seemingly good results with sulfadiazine, only to observe recurrences of lesions several months and two years later. The same authors reported improvement with sulfadiazine in two cases of pulmonary cryptococcosis, although death followed in one. They referred to three cases of Baker's and one of Dormer's group being treated successfully with surgical resection.[3] Fisher, in his review, has adequately dealt with the question of therapy. Iodides were formerly employed but with unsatisfactory results, except in an occasional case. Results with sulfonamides, according to Fisher, again have been variable and on the whole discouraging.[1] Eisen et al. only recently reported a case with involvement of the third lumbar vertebra and lungs. The patient was given sulfadiazine with regression of the mass at the level of the third lumbar vertebra with ultimate removal of the spinous process. There was clearing of the lung lesion, and the patient was reportedly well six years after onset.[4]

In an early report on penicillin, Dawson and co-workers stated that the drug was effective in vitro. However, subsequent studies in vitro and in mice gave little if any promise of its therapeutic efficacy.[1]

Carton reported on the use of cycloheximide (Actidione) in this condition. Of four of his own cases, two showed improvement, one of which was considered an apparent cure. He reviewed 12 other cases. No data were available in one. Three cases had apparent remissions. One patient died with negative cultures. Two patients died with a "reduction in the number of organ-

isms." Four others had clinical improvement but died, and one other died without any response.[5]

Norris reported the use of methylrosaniline chloride (gentian violet) along with potassium iodide, hexylresorcinol and tetracycline in cryptococcosis involving the nasal passages.[6] Although improvement occurred, occasional nasal discharge was obtained, and further culture of material was not attempted.

Line used a total of 3.5 gm. of ethyl vanillate in a case of intracranial cryptococcosis and had a remission of six months' duration with a negative culture during this time, only to have death occur with a positive culture.[7]

Of late, another group of compounds, the diamidines, have been found to be active against various fungi. Chief of this group are the drugs: propamidine, stilbamidine and 2-hydroxystilbamidine. Numerous in vitro and animal experiments have been performed using C. neoformans as the organism. Fisher reported the use of propamidine against two strains, with the organism being killed by dilutions as low as 0.062% and with inhibition at dilutions of 0.008%. In vivo tests showed no inhibition of growth. Taschdjian found that stilbamidine dihydrochloride and diisethionate, as well as 2-hydroxystilbamidine, prevented growth of the organism at concentrations of 100γ per milliliter of media. At a pH of 7, in serial dilutions, growth was inhibited at only 600γ per milliliter. This author also reported disappointing results in vivo.[8] Christison found that stilbamidine did not inhibit C. neoformans but found inhibition at levels of 2.5 mg. per 100 cc. with propamidine and pentamidine.[9] Bocabo noted inhibition with stilbamidine and propamidine only with amounts greater than 1000γ.[10] Fahlberg found no inhibition by stilbamidine, incomplete inhibition at 100γ per milliliter of propamidine, and complete inhibition at 100γ per milliliter of pentamidine.[11] In our own case we found inhibition with stilbamidine at 500γ per milliliter, with 2-hydroxystilbamidine and aminostilbamidine at 250γ and propamidine at 100γ per milliliter.

Miller et al., using intracranially and intraperitoneally infected mice, found no results with stilbamidine at doses of 100 and 500 mg. per kilogram.[12] Schoenbach was able to control infections in mice with doses of 250 to 500 mg. per kilogram of stilbamidine but felt that the organism was resistant at concentrations obtainable clinically.[13]

In a review of the literature we have found only three case reports where the diamidines have been used. There is only one case where 2-hydroxystilbamidine has been used and apparently with success. Whitehill and Rawson have reported an apparent cure with 2-hydroxystilbamidine.[16] Their case was a 16-year-old Negro girl who had adenopathy and hepatosplenomegaly and was treated with 4.05 gm. of the drug over a period of 19 days. She was discharged asymptomatic and apparently had remained so on reaxamination four and one-half months later. This case and our own are certainly encouraging, although follow-up examination in both instances has been relatively short. Miller et al. reported three cases in which stilbamidine was used in dosages of 3.75, 1.05, and 1.34 gm., with no change in one and death ensuing in the other two cases.[14] Bacon et al. used 1.25 gm. of stilbamidine in a case of meningoencephalitis due to this organism with no apparent change. Sulfadiazine and cycloheximide also did not help in this case.[15]

It is interesting that reports have appeared in the literature concerning the association of cryptococcosis with conditions involving the reticuloendothelial system. Fisher reported on a case of generalized cryptococcosis in which a biopsy of a lymph node showed typical changes of Boeck's sarcoid, including Schaumann bodies.[1] Gandy also reported a case of cutaneous cryptococcosis in which histological study had led to a diagnosis of sarcoid.[19] Conant et al., quoted Cawley and workers on the coexistence of myelogenous, lymphatic, and monocytic leukemia with cryptococcosis.[3] Gendel et al. reported 1 case and reviewed 13 others in which cryptococcosis coexisted

with Hodgkin's disease.[20] Nichols et al., in reviewing nine cases seen by them, point out that the reticuloendothelial system is probably always involved at some time in the disseminated form of cryptococcosis. Enlarged lymph nodes have been mentioned in nearly 20% of reported cases, and at postmortem examinations the liver and spleen are often found to contain lesions. Moreover, only on occasion have cryptococci been isolated from these nodes, and the importance of making cultures of such material is emphasized. That the problem is complicated is brought out by three cases in which biopsies were obtained. In one case the diagnosis of Hodgkin's disease was reconfirmed on reexamination of a node, while it was not reconfirmed in another. In a third case the microscopic appearance of the node was that of a noncaseating granuloma, suggestive of sarcoidosis.[23]

Collins and his group point out that when an inflammatory response is excited by the organism, the granulomatous reaction may contain multinucleated giant cells, lymphocytes, eosinophils, plasma cells, monocytes, and a varying degree of fibroblastic reaction with occasional development of tubercles and areas of necrosis.[21] They also warn that frequently the organism can be recognized only with the greatest difficulty, if at all, even though it has been identified by fresh smear or culture of the tissue. It is their opinion that cryptococcosis is capable of producing a lymphadenopathy that in some instances could closely simulate another disease of the reticuloendothelial system. Other authors in studying tissue changes in cryptococcosis have also observed the lack of neutrophilic response and abscess formation in the majority of cases and classify the cryptococcal organism as being a foreign-body irritant rather than a producer of acute inflammation.[22]

Our interest in this aspect of the disease has been stimulated by the existence of cryptococcosis and sarcoidosis in our patient. A biopsy of a lymph node taken early in the course of this man's illness was interpreted as Boeck's sarcoid or hyperplastic tuberculosis. After treatment for cryptococcosis, followed by complete healing at the sites where positive cultures were obtained, involvement of the reticuloendothelial system progressed. Multiple biopsies of nodes and the spleen also were interpreted as Boeck's sarcoid or hyperplastic tuberculosis. Cultures of these materials were negative for cryptococci and acid-fast bacilli. An epithelioid reaction developed at the site of injection of the Kveim material and was interpreted as a positive test. Sitzbach and Ehrlich report a high correlation of positive Kveim tests with the clinical diagnosis of sarcoid and only 4% false-positive reactions.[18]

The pulmonary lesion on x-ray was described as sarcoid or old arrested tuberculosis. Evans and Harrell point out that small nodular shadows suggesting miliary tuberculosis may be seen in cryptococcosis. After healing, small amounts of fibrosis remain, and the lymphatic structure in the hilar region may show slight enlargement.

The possibility that sarcoidosis existed in this patient long before he became infected with cryptococcus must be considered. The progression of involvement, particularly of the reticuloendothelial system, the benignity of the process, and the inability to culture organisms leads us to feel that we were dealing with a case of sarcoidosis complicated by cryptococcosis. A period of 15½ months has elapsed since completion of 2-hydroxystilbamidine therapy, and we have found no evidence of recurrence of the cryptococcal infection. In view of this we feel justified in considering this case an apparent cure.

Summary

A case of Boeck's sarcoid complicated by cryptococcosis and treated with 2-hydroxystilbamidine is presented. A review of the therapy of this disease with particular emphasis on in vitro and in vivo experimentation as well as clinical experience with the aromatic diamidines is briefly covered. A discussion of the association of cryptococco-

sis with other diseases of the reticuloendothelial and lymphatic systems is included.

Veterans Administration Hospital (Dr. Baker).

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The Sensitivities and Cross Resistances of Gram-Negative Bacilli to Antibiotics

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This report is an attempt to present data regarding the sensitivities of Gram-negative bacilli to antibiotics in a manner that will be of maximum use to practicing physicians. Experience at the Milwaukee County General Hospital has shown that many cases of severe infections must be treated with antibiotics before the results of sensitivity tests are available to the ward physician. In these cases therapy which has been based on previous experience regarding the sensitivities of bacteria to the antibiotics usually has been successful. As a result of this experience the majority of cases of infections are now treated successfully with antibiotics that are selected on the basis of statistical studies rather than by specific sensitivity tests on each causative strain of bacteria. This has markedly reduced the number of sensitivity studies that must be done by the laboratory and allowed us to use the highly sensitive tube-dilution method for determining bacterial sensitivity to antibiotics in problem cases in which precise knowledge both of bactericidal activity and of combinations of drugs is necessary. Since studies of bacterial sensitivity to antibiotics which were done at widely spaced laboratories have not been markedly different, these data derived at the Milwaukee County General Hospital can be expected to be applicable to the treatment of infections due to Gram-negative bacilli in other locals.[1-3] It is for this reason it was felt to be worthy of presentation.

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Materials and Methods

Four hundred ten strains of Gram-negative bacilli were tested for their sensitivity to the antibiotics by the tube-dilution method.[4,5] Each strain had been isolated between the years 1951 and 1956 from an infection at the Milwaukee County General Hospital. Bacteriostatic endpoints were used throughout the study.[5] An inhibitory concentration of each antibiotic was chosen that we felt represented a level that would usually indicate a clinical response would be achieved if the patient were given that antibiotic. These crucial levels were selected on the basis of clinical experience as well as on the basis of the relative concentrations of the drugs that result from administration of usual doses.[6-11] Three micrograms per milliliter or less was considered to represent an inhibitory concentration that would correlate with clinical sensitivity to the tetracyclines, polymyxin B, penicillin, and neomycin. Twenty-five micrograms per milliliter were chosen as the crucial levels for chloramphenicol and nitrofurantoin. The following information was determined from all the data and will be presented in tabular form:

1. The rank of each antibiotic against Escherichia coli, Aerobactor aerogenes, Pseudomonas aeruginosa, Proteus, Pseudomonas species, and a mixture of all these species of Gram-negative bacilli.

2. The antibiotic most likely to be effective against strains resistant to another antibiotic. This information was determined by grouping the strains of each species that was resistant to each of the antibiotics and determining what percentages of each of these groups of resistant organisms were sensitive to each of the other antibiotics.

3. The best theoretical combinations of antibiotics against each species of the Gram-negative bacilli and against a mixture of equal numbers of the various species. These combinations were made up by selecting the antibiotic most effective against each of the species that were being tested and adding to it the drug that was effective against the greatest percentages of strains resistant to the first agent. These combinations were not selected on the basis of possible potentiating or additive effects but rather on a basis of increasing the

TABLE 1.—*Relative Activity of Antimicrobial Drugs Against E. Coli*

Rank	Drug	Strains Sensitive to Each Drug, per Cent
1	Chloramphenicol	91 (39)*
2	Nitrofurantoin	85 (25)*
3	Chlortetracycline	74
4	Neomycin	71
4	Tetracycline	71
4	Oxytetracycline	71
5	Polymyxin B	60
6	Streptomycin	29
7	Penicillin	7

*The numbers in parenthesis represent the per cent of strains sensitive to 3 γ per milliliter of chloramphenicol and nitrofurantoin. This gives the weight for weight comparison of these drugs with the other antibiotics.

theoretic antimicrobial spectrum against each of the species that was being tested.

4. Changes in the sensitivities of the species of Gram-negative bacilli between the years 1951 and 1955. The sensitivities to each of the antibiotics of the first 20 strains of each species isolated in 1951 and in 1956 were compared. The means of the serial dilutions necessary for inhibition were compared, and a statistical analysis of the differences between the means was made by the use of the Student T-value Tables.[12] A significant difference in the sensitivity of a species to an antibiotic was considered to have occurred when the difference between the means was of great enough magnitude to occur by chance in less than one time in a hundred (P-value less than 0.01).[12]

Results

1. The rank of each antibiotic against E. coli, A. aerogenes, P. aeruginosa, Proteus, Pseudomonas species, and a mixture of all of these species of Gram-negative bacilli.

E. coli.—Table 1 shows that the majority of strains of these species are sensitive to the so-called "wide-spectrum" antibiotics, with the exception of streptomycin. This is consistent with our clinical experience in which we have rarely encountered an infection due to an E. coli that was a severe problem to treat because of antibiotic resistance of the organism. At present we treat the majority of infections without obtaining a specific sensitivity test. We have rarely encountered the type of infection in the hospital described by Kirby,[13] in which antibiotic-resistant E. coli were the offending organisms.

TABLE 2.—*Relative Activity of Antimicrobial Drugs Against A. Aerogenes*

Rank	Drug	Strains Sensitive to Each Drug, per Cent
1	Neomycin	70
2	Chloramphenicol	62 (14)*
3	Oxytetracycline	44
4	Polymyxin B	37
5	Chlortetracycline	36
6	Tetracycline	33
7	Streptomycin	32
8	Nitrofurantoin	29 (16)*
9	Penicillin	7

*See footnote to Table 1.

A. aerogenes.—This species is relatively more resistant to antibotics than its close relative E. coli (Table 2). Fortunately 77% of strains respond to either chloramphenicol or oxytetracycline (Table 3). However, in many cases sensitivity studies of a particular strain are necessary for the determination of the best antibiotic for a particular patient.[14]

TABLE 3.—*The Optimal Theoretical Combinations of Antibiotics Against Each Species of Gram-Negative Bacilli*

Species	Combination	Strains Theoretically Susceptible, per Cent
P. aeruginosa	Polymyxin B and either oxytetracycline or tetracycline	81
Proteus	Chloramphenicol and tetracycline	91
E. coli	Chloramphenicol and polymyxin B	97
A. aerogenes	Chloramphenicol and oxytetracycline	77
Pseudomonas species	Chloramphenicol and polymyxin B	67
Mixture of species	Chloramphenicol and polymyxin B	83

Proteus.—The strains of Proteus that were studied were not keyed down to the specific subspecies but represent the Proteus that have caused infections in our hospital during the past five years. The data in Table 4 are presented as a mixed group of Proteus, since most hospital laboratories do not key down this species, and therefore the Table will be of maximum use to clinicians who receive a report from their laboratory of Proteus rather than a specific species of Proteus organisms. Table 4 shows chloramphenicol to be the drug of choice against these bacilli, with the other agents being rarely of value. Table 3 shows that many Proteus resistant to chloramphenicol are sensitive to tetracycline, and this must be considered the combination of agents to use in a

TABLE 4.—*Relative Activity of Antimicrobial Drugs Against Proteus*

Rank	Drug	Strains Sensitive to Each Drug, per Cent
1	Chloramphenicol	78 (7)*
2	Penicillin	38
3	Neomycin	36
4	Tetracycline	34
5	Nitrofurantoin	33 (4)*
6	Streptomycin	20
7	Chlortetracycline	10
8	Oxytetracycline	5

*See footnote to Table 1.

fulminating infection. When the Proteus were keyed down our results confirmed those of Finland, who pointed out that penicillin was particularly effective against Proteus mirabilis.[15]

P. aeruginosa.—This species is at present the most resistant to antibiotics, and it is fortunate that most infections due to this organism are benign (Table 5). Polymyxin B, the antibiotic of choice, appears to be becoming less effective against aeruginosa, and in addition the painfulness of the intramuscular injection of this antibiotic makes it difficult to administer other than by the topical route. In severe fulminating infections we give 100 mg. of polymyxin B in 300 ml. of 5% dextrose in water by the intravenous route twice daily. The combination of oxytetracycline or of tetracycline with polymyxin B was active against 81% of the strains tested and should be used in severe infections (Table 3). The resistance of a high percentage of strains of P. aeruginosa to chlortetracycline, chloramphenicol, and nitrofurantoin explains why this organism is so often a secondary invader when any of these agents are given (Table 3). Persistant urinary tract infections in which P. aeruginosa is the infecting

TABLE 5.—*Relative Activity of Antimicrobial Drugs Against P. Aeruginosa*

Rank	Drug	Strains Sensitive to Each Drug, per Cent
1	Polymyxin B	72
2	Oxytetracycline	39
3	Neomycin	38
4	Tetracycline	16
5	Streptomycin	9
6	Chlortetracycline	9
7	Chloramphenicol	8 (4)*

*See footnote to Table 1.

organism are commonly found in all large clinics, and the fact that this organism is of low pathogenicity as well as that it has antibacterial activity in its own right should help us to rationalize our inability to eradicate it in many cases.[1,5,8]

Pseudomonas Species.—A group of organisms that in most ways resemble P. aeruginosa but that do not produce pigment our laboratory classifies as Pseudomonas species. These organisms also differ from P. aeruginosa by usually being resistant to polymyxin B (Table 6). Chloramphenicol is the most effective agent against this group of bacteria, but as in the case of P. aeruginosa, many urinary tract infections due to this organism are refractory to all therapy. Table 3 illustrates the fact that the optimal combination of antibiotics against Pseudomonas species, chloramphenicol and polymyxin B, is effective against only 67% of the strains.

TABLE 6.—*Relative Activity of Antimicrobial Drugs Against Pseudomonas Species (Non-Dye-Formers)*

Rank	Drug	Strains Sensive to Each Drug, Per Cent
1	Chloramphenicol	57 (4)*
2	Tetracycline	38
3	Neomycin	38
4	Nitrofurantoin	26 (0)*
5	Oxytetracycline	24
6	Chlortetracycline	22
7	Polymyxin B	20
8	Streptomycin	6
9	Penicillin	2

*See footnote to Table 1.

The relative activity of antimicrobial agents against a mixed group of Gram-negative bacilli which included 50 strains each of E. coli, A. aerogenes, Proteus, P. aeruginosa, and Pseudomonas species is shown in Table 7. This Table was constructed to be of aid when a Gram stain from a blood culture showed Gram-negative bacilli and when the patient's condition was such that treatment was imperative before the organism could be positively identified. In this situation neomycin and chloramphenicol would be the drug of choice, or, if a combination of agents were desired, chloramphenicol and polymyxin B would give

TABLE 7.—*The Relative Activity of the Antibiotics Against a Mixed Group of Gram-Negative Bacilli, Which Includes E. Coli, A. Aerogenes, Proteus, P. Aeruginosa, and Pseudomonas Species*

Rank	Antibiotic	Strains Sensitive, per Cent
1	Neomycin	64
2	Chloramphenicol	59
3	Polymyxin B	51
4	Oxytetracycline	40
4	Nitrofurantoin	40
5	Tetracycline	36
6	Chlortetracycline	32
7	Streptomycin	22
8	Penicillin	17

TABLE 8.—*The Activity of Tetracycline Against Gram-Negative Bacilli*

Bacteria	Per Cent Sensitive
E. coli	74
Pseudomonas species	38
Proteus	34
A. aerogenes	33
P. aeruginosa	16

TABLE 9.—*The Activity of Chloramphenicol Against Gram-Negative Bacilli*

Bacteria	Per Cent Sensitive
E. coli	91
Proteus	78
A. aerogenes	62
Pseudomonas species	57
P. aeruginosa	8

TABLE 10.—*The Activity of Nitrofurantoin Against Gram-Negative Bacilli*

Bacteria	Per Cent Sensitive
E. coli	85
Proteus	33
A. aerogenes	29
Pseudomonas species	26
P. aeruginosa	0

TABLE 11.—*The Activity of Polymyxin B Against Gram-Negative Bacilli*

Bacteria	Per Cent Sensitive
P. aeruginosa	72
E. coli	67
A. aerogenes	37
Pseudomonas species	20
Proteus	0

TABLE 12.—*The Activity of Oxytetracycline Against Gram-Negative Bacilli*

Bacteria	Per Cent Sensitive
E. coli	71
A. aerogenes	44
P. aeruginosa	39
Pseudomonas species	24
Proteus	5

TABLE 13.—*The Activity of Neomycin Against Gram-Negative Bacilli*

Bacteria	Per Cent Sensitive
E. coli	77
Proteus	77
A. aerogenes	70
P. aeruginosa	38
Pseudomonas species	37

the widest antimicrobial spectrum (Tables 3 and 7).

Tables 8 through 15 are presented to emphasize the fact that there are marked differences between each of the antimicrobial agents. The tetracyclines in particular have often been considered interchangeable, and Tables 8, 12, and 14 show that oxytetracycline is clearly superior to tetracycline and chlortetracycline against P. aeruginosa and that tetracycline is probably superior to the other two agents against Proteus and Pseudomonas species. Neomycin and chloramphenicol appear to have the widest antimicrobial effect, as was already pointed out in Tables 1 through 7.

2. The antibiotic most likely to be effective against a strain of Gram-negative bacilli resistant to another antibiotic.

Table 16 is an arrangement of data that have been particularly useful when we have been confronted with a patient who was crucially ill and who was not responding to antibiotic therapy. In these cases precise identification and studies of the infecting organism of course are indicated, but while this information is being gathered the changing of therapy on the basis of Table 16 will

TABLE 14.—*The Activity of Tetracycline Against Gram-Negative Bacilli*

Bacteria	Per Cent Sensitive
E. coli	74
Pseudomonas species	38
Proteus	34
A. aerogenes	33
P. aeruginosa	16

TABLE 15.—*The Activity of Chlortetracycline Against Gram-Negative Bacilli*

Bacteria	Per Cent Sensitive
E. coli	74
A. aerogenes	36
Pseudomonas species	22
Proteus	10
P. aeruginosa	9

TABLE 16.—*The Antibiotics to Administer When There Is No Response to Another Antibiotic*

Antibiotic to Which There is No Response	Antibiotic to Which to Change	
	1st Choice	2nd Choice
Chloramphenicol	Polymyxin B	Neomycin
Neomycin	Tetracycline	Chloramphenicol
Nitrofurantoin	Chloramphenicol	Tetracycline
Polymyxin B	Nitrofurantoin	Tetracycline
Tetracycline	Neomycin	Nitrofurantoin
Oxytetracycline	Chloramphenicol	Neomycin
Chlortetracycline	Polymyxin B	Chloramphenicol
Penicillin	Chloramphenicol	Nitrofurantoin
Streptomycin	Nitrofurantoin	Chloramphenicol

often give the patient the best statistical chance of survival by showing what antibiotic has the best chance of being active against a strain of bacteria resistant to another antibiotic.

3. The best theoretical combinations of antibiotics against each species of the Gram-negative bacilli and against a mixture of equal numbers of the various species.

Table 3 was devised because of the fact as brought out by our data (see above) that no one antimicrobial agent is truly wide-spectrum. Thus we feel that every patient with severe sepsis should be treated initially with more than one drug. Table 3 presents the combination of agents most likely to be effective against each species of the Gram-negative bacilla and against infections when the causative bacteria are not postively identified.

4. Changes in the sensitivities of the species of Gram-negative bacilla between the years 1951 and 1955.

It is apparent from Table 17 that the Gram-negative bacilli have remained relatively stable in regard to sensitivity to antibiotics. In only four instances did organisms become more resistant (Table 17), and in three of these they became more resistant to polymyxin B, a drug that is rarely used at the Milwaukee County General Hospital. It is of interest also that in six instances species became more sensitive to antibiotics. These data suggest that the significant differences that were noted were due to evolutionary type changes among the bacteria and were not directly related to the use of antibiotics within the hospital.

Comment

This study is an example of one use to which data can be put that were originally gathered to direct therapy of individual patients. We have been able to reduce markedly the number of tests done on bacteria isolated from the individual patients by relying on our past experience in the majority of cases. Thus when a particular case demands precise meticulous study, personnel and facilities are available to study new agents, bactericidal end-points, and combinations of drugs.[6] In addition we have been able to dispense with all "disc type" sensitivity tests which in our and others' experience have not been as accurate and dependable, as the tube-dilution method for determining the sensitivity of bacteria to antibiotics.[16] It is our conviction that patients will more likely receive optimal therapy if they are treated on a basis of a statistical method derived from tube-dilution studies than if they are treated on a basis of the results of disc sensitivity tests. It is only fair to point out, however, that many authorities disagree with this viewpoint.[17,18]

A study of the Tables reveals also the ineffectiveness of the popular combination of antibiotics, streptomycin, and penicillin. It can be noted that by far the great majority of Gram-negative bacilli are resistant

TABLE 17.—*Significant Changes in the Sensitivity of Gram-Negative Bacilli to Antibiotics Between 1951 and 1955*

Increase in Resistance		Decrease in Resistance	
Species	Antibiotic	Species	Antibiotic
P. aeruginosa	Polymyxin B	P. aeruginosa	Neomycin
E. coli	Polymyxin B	Proteus	Chlortetracycline
A. aerogenes	Polymyxin B	Proteus	Neomycin
A. aerogenes	Oxytetracycline	Proteus	Oxytetracycline
		Proteus	Streptomycin
		E. coli	Neomycin

to both of these agents, and therefore the use of this combination for "wide-spectrum" coverage indeed is on shaky ground.

The important differences between even closely related antibiotics are emphasized by this report, and this adds support to recent warnings against considering the so-called wide-spectrum antibiotics as interchangeable.[19,20] The two most important distinctions between the tetracycline group and chloramphenicol appear to be the particular effectiveness of oxytetracycline against P. aeruginosa and the effectiveness of chloramphenicol not only against Micrococcus pyogenes but also against Proteus and Pseudomonas species.

The change in the sensitivities of these Gram-negative bacilli to antibiotics within a four-year period were not marked and were in counterdistinction with published experience regarding M. pyogenes. This may be due to the fact that many M. pyogenes infections develop in the hospital, whereas the majority of infections due to Gram-negative bacilli develop elsewhere. The fact that some organisms became significantly more resistant to seldom-used antibiotics suggests that other factors than selective pressures induced by antibiotic usage play a role in changes in the antibiotic resistance of bacteria. The lack of very significant changes in the antibiotic sensitivity of the Gram-negative bacilli found by us is somewhat at variance with the report of Sanford, Favour, and Mao, who compared 250 recent cultures with 27 lyphilized cultures of Gram-negative bacilli isolated before 1946.[21] The disparity between the numbers in their control and recent cultures might be the explanation for the lack of agreement. In addition we used a *P*-value of 0.01 as being of significance, and they used a *P*-value of 0.02 for their criteria of significance.

The potential use of data such as have been presented in the treatment of mass casualties is apparent. In a hypothetical situation in which thousands of persons would be exposed to radiation and its attendant infections therapy would have to be selected on a statistical basis, and changes in therapy would have to be directed by a precise knowledge of cross resistance.[22] Therefore, studies such as this should be done in various large hospitals throughout the country. These would be of help not only in the treatment of mass casualties but in the rational procurement of stockpiles of antibiotics which must be held in reserve for possible disaster.

Summary and Conclusions

The results of tests of the sensitivity to antibiotics of 434 strains of Gram-negative bacilli isolated at the Milwaukee County General Hospital are presented and tabulated. Changes in the antibiotic sensitivity of strains isolated in 1951 and 1955, the relative activity of each antibiotic against P. aeruginosa, A. aerogenes, Proteus, Pseudomonas species, and E. coli, the antibiotic most likely to be effective when another antibiotic has failed, and the best combination of antibiotics to use in order to obtain a wide spectrum are presented.

These results should be of aid for the initiation of therapy in cases in which specific studies are not available or completed and also should have applications in the planning of the care of mass casualties in whom secondary bacterial infections will be of major importance.

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An Evaluation of Lymphadenopathy in Systemic Disease

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Biopsy of lymph nodes is frequently required in patients with lymphadenopathy when other routine investigative procedures are not diagnostic. In many instances the histologic pattern is characteristic of a particular disease. However, in a significant number of cases, the histologic changes are not diagnostic. Often this latter group of patients have manifestations of acute, severe disease or an illness which is insidious but progressive. In some the disease is fatal. Thus, the clinician has the problem of therapy and prognosis in severe, but undiagnosed illness.

The present study represents an attempt to determine the ultimate course of the illness of patients in whom biopsy of lymph nodes was not diagnostic. It was also decided to reexamine the material from biopsy of lymph nodes to determine whether there was recognizable relationships between the histologic or cytologic changes in the nodes and the diseases which developed.

Materials and Methods

All patients who had had biopsies done on enlarged superficial lymph nodes at University Hospitals from 1945 to 1955 were included in this series. Some were relatively asymptomatic at the time of biopsy. Others had manifestations of generalized disease, such as fever, loss of weight, anemia, or malaise. No material removed during radical dissection from known malignancy or during surgical exploration of the cavities of the body was included.

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TABLE 1.—*Specific Diagnoses of Material Taken on Biopsy of Lymph Nodes in 201 Patients, 1945-1954 Inclusive*

Carcinoma, all types	81
Lymphoma, all types	64
Tuberculosis	32
Sarcoidosis	14
Melanoblastoma	5
Myxosarcoma	1
Amyloidosis	1
Malignancy, type unspecified	3
	201

From a total of 379 patients, 201 had specific histopathologic diagnoses (Table 1) with good clinical correlation. At the time of the original examination, the material from biopsy of lymph nodes from the remaining 178 patients had been diagnosed as showing atypical hyperplasia, hyperplasia, lymphadenitis, or nonspecific granuloma, or as normal. Fourteen patients were dropped from this series because of inadequate clinical follow-up or loss of tissue. An additional six cases were excluded because, on review of the original sections, a diagnosis of lymphoma was made.

The clinical course was determined in the 158 remaining patients. This was done by review of the hospital records; and by personal interviews with the patient, his physician, or an immediate member of his family. The duration of the follow-up ranged from 1 to 11 years.

The histologic sections from the 158 cases were examined without knowledge of the clinical findings or previous histopathologic diagnosis. The original sections had been stained with hematoxylin and eosin. Additional slides were prepared from the paraffin blocks and the hematoxylin and eosin stains repeated. In addition, a periodic-acid-Schiff (PAS) reaction[1] was performed. In some

TABLE 2.—*Clinical Follow-Up (One to Eleven Years) of 158 Patients*

Living and well	47
Living with disease	56
Deceased	55
	158

TABLE 3.—*Correlation of Ultimate Clinical Diagnosis with Review of Pathologic Diagnosis (Number of Cases)*

Ultimate Clinical Diagnosis	Hyperplasia	Inflammation	Normal Histology	Total	Increase Plasma Cells with PAS + Cytoplasm	PAS+ Intracytoplasmic Inclusion Bodies
Collagen disease						
Disseminated lupus erythematosus	14	0	0	14	14	14
Dermatomyositis	2	0	0	2	2	0
Polyarteritis nodosum	1	0	0	1	1	0
Rheumatoid arthritis	5	0	0	5	3	1
Rheumatic fever	1	0	0	1	1	0
Rheumatic heart disease	1	0	0	1	1	0
Unknown type	2	0	0	2	2	1
Malignancy						
Carcinoma, all types	20	2	2	24	11	2
Leukemia—lymphoma	10	0	0	10	0	0
Melanoblastoma	2	0	0	2	1	0
Multiple myeloma	1	0	0	1	1	0
Dermatoses						
Acanthosis nigricans, benign type	1	0	0	1	1	1
Exfoliative dermatitis	2	0	0	2	2	0
Erythema nodosum	1	0	0	1	0	0
Hypersensitivity to contactants and ingestants	4	0	0	4	4	0
Neurodermatitis	1	0	0	1	0	0
Eczematoid dermatitis	1	0	0	1	1	0
Dermatitis, chronic, type unknown	2	0	0	2	2	0
Other existing disease						
Tuberculosis	3	2	0	5	0	0
Sarcoidosis	3	0	0	3	0	0
Chronic nontuberculous pulmonary disease	5	1	0	6	2	1
Primary cardiovascular disease (AS, ASHD, HCVD)	5	0	0	5	0	0
Primary bone disease*	2	1	1	4	0	0
Undiagnosed disease	4	0	1	5	2	0
Miscellany†	5	2	1	8	1	0
Living and well	39	8	0	47	12	2
Totals	137	16	5	158	64	22

* Osteomyelitis, osteoarthritis, lipochondrodystrophy, fibrous dysplasia.
† Histoplasmosis, syphilis, diabetes mellitus, sickle-cell anemia, polycythemia vera.

instances material from autopsies was available and was subsequently reviewed.

Results

The results of the investigation of the 158 patients with lymphadenopathy of nondiagnostic type are summarized in Tables 2 and 3. Forty-seven of the patients are living and well. Fifty-six are living, with specific disease entities diagnosed within one year of biopsy. In most of this latter group, lymphadenopathy has persisted, but, in many instances, without apparent relationship between the systemic disease and the lymphadenopathy. Fifty-five of the one hundred fifty-eight patients are dead, and in twenty-six of these cases an autopsy was performed. It was noteworthy that 18 patients died of carcinoma, 9 of lymphoma, and 15 of "collagen disease."[2]

Because of lymphadenopathy, biopsies were done on 10 of the 37 patients with malignancy to determine the presence of metastases of already known carcinoma. The remaining 27 patients subsequently had the diagnosis of malignancy proven by further surgical procedures or at autopsy.

It is significant that 26 patients developed recognizable illnesses that are sometimes categorized as "collagen disease"[2] (Table 3). Seven of these had clinical findings consistent with disseminated lupus erythematosus and a positive L. E. test.[3] Two of these seven patients subsequently showed typical tissue changes of this disease at autopsy. Seven additional patients with a disease entity consistent with that of disseminated lupus erythematosus occurred before the advent of the L. E. test. Of these seven cases, the diagnosis was confirmed at autopsy in five instances.

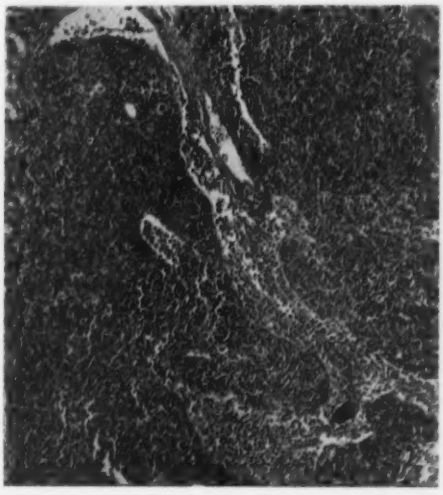
Both patients with dermatomyositis are dead, but in only one instance was an autopsy performed. The case of polyarteritis was confirmed at postmortem examination. There were good x-ray and physical signs of rheumatoid arthritis in the five patients with this diagnosis, all of whom are living. There was one patient with rheumatic fever and one with rheumatic heart disease.

Two patients, who are still living, were classified as having "collagen disease," type unknown. One of these clinically resembles polyarteritis nodosa, and the other has features of both disseminated lupus erythematosus and polyarteritis. These two patients have negative L. E. preparations.

A study of the lymph nodes of patients in whom a diagnosis of "collagen disease" seemed appropriate demonstrated the presence of specific histologic changes in cases of lupus erythematosus. Early, as the cellularity of the node increased, there was progressive loss of distinction between the cortex and medulla. The follicles increased in number and size but remained well defined, with prominent secondary centers. Here the cells varied in maturity. Mitotic figures were frequent, but nuclear debris was absent. There was moderate to marked hyperplasia of the reticuloendothelial cells (Fig. 1), with occasional multinucleation. Erythrophagocytosis by these cells was prominent.

Within the pulp of the lymph node there was an increase in immature lymphocytes, and mitotic figures were frequent. Large, abnormal cells with acidophilic cytoplasm

Fig. 1.—Cortex of a lymph node from a biopsy specimen from a patient with disseminated lupus erythematosus which illustrates prominent sinusoidal pattern and cellularity of pulp. Hematoxylin and eosin; × 65.



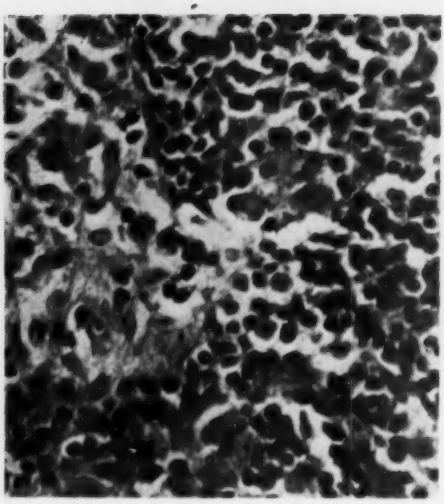


Fig. 2.—Material taken on biopsy of a lymph node from a patient with disseminated lupus erythematosus which illustrates prominent sinusoidal cells, plasma cells scattered amidst the lymphocytes of the pulp, and a cell with an inclusion, which has displaced and compressed the nucleus. Hematoxylin and eosin; × 450.

and one to several deeply basophilic, coarsely granular nuclei were also present. These latter cells were compared to megakaryocytes by Fox and Rosahn [4] when they first described them in the lymph nodes of patients with disseminated lupus erythematosus. Plasma cells were increased [5,6] in all the lymph nodes examined and were in greatest concentration within and adjacent to the sinusoids (Fig. 2). Eosinophiles were few or absent. There was no necrosis or acute inflammation in any of the material taken from lymph nodes.

Later the follicles became less prominent and in the tissue from autopsies were markedly decreased in number or completely absent. The hyperplasia of the reticuloendothelial elements decreased in amount, as indicated by the fact that the lymph nodes at the time of death revealed only slight prominence of the sinusoidal cells (Fig. 3). Also, a marked decrease in the number of lymphocytes in the pulp of the node with further increase in plasma cells was apparent (Fig. 4).

These changes are consistent with lupus erythematosus but not diagnostic. However, with one additional finding they are almost specific. This is the presence in sections stained with hematoxylin and eosin of a faintly eosinophilic inclusion within the cytoplasm of some of the plasma cells (Fig. 2). Rarely, such cells are numerous, but

Fig. 3.—Cortex of a lymph node at autopsy from a case of disseminated lupus erythematosus which illustrates loss of prominence of sinusoids and less cellularity of pulp. Hematoxylin and eosin; × 65.

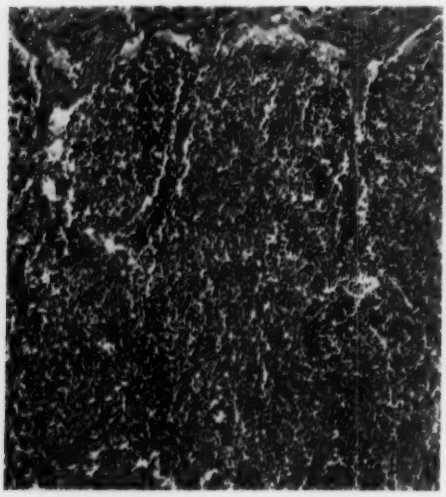
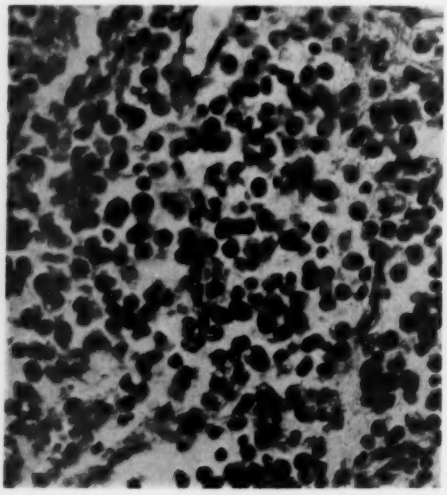


Fig. 4.—Lymph node at autopsy from a case of disseminated lupus erythematosus which illustrates loss of prominence of the sinusoidal cells and marked increase in the number of plasma cells. Hematoxylin and eosin; × 450.



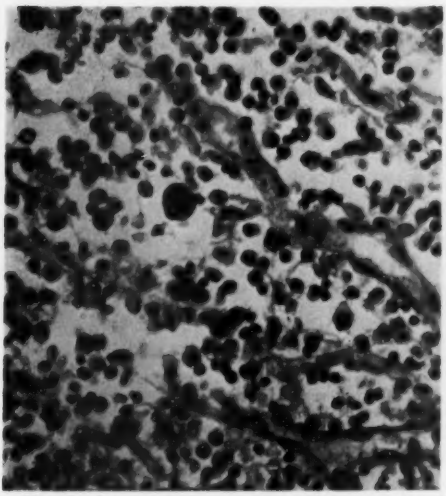


Fig. 5.—Lymph node at autopsy from a case of disseminated lupus erythematosus which shows a typical cellular inclusion, which has displaced the nucleus. Periodic acid Schiff reaction; × 450.

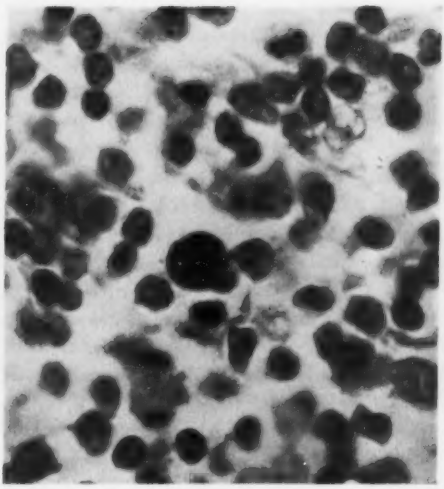


Fig. 6.—Material taken on biopsy of a lymph node from a patient with disseminated lupus erythematosus which illustrates a typical inclusion. Periodic acid Schiff; × 1000.

usually a thorough search of the tissue is required for their recognition. This characteristic structure is frequently single and homogeneous and tends to push the nucleus to one side (Figs. 5 and 6). Occasionally it appears to be composed of several oval masses clustered together within the cytoplasm (Fig. 7). When the PAS technique is used, the cellular inclusion is easily seen because of the intense red reaction.

By the use of the PAS procedure, a gradual evolution of this intracytoplasmic inclusion may be inferred. Initially, the diffuse PAS-positive reaction of the cytoplasm of many of the plasma cells is intense. Occasional cells show the formation of one

Fig. 7.—Lymph node at autopsy from a case of disseminated lupus erythematosus which shows a cluster of inclusions in which no nuclear material is identified. Periodic acid Schiff reaction; × 450.

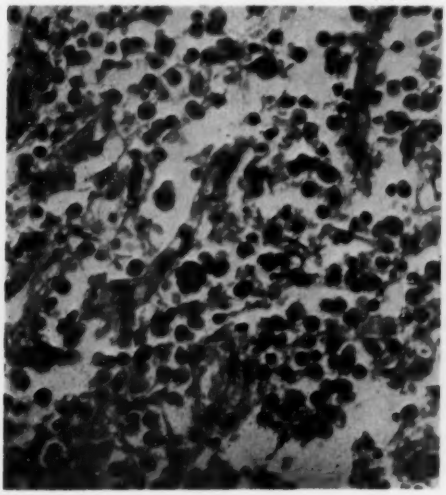
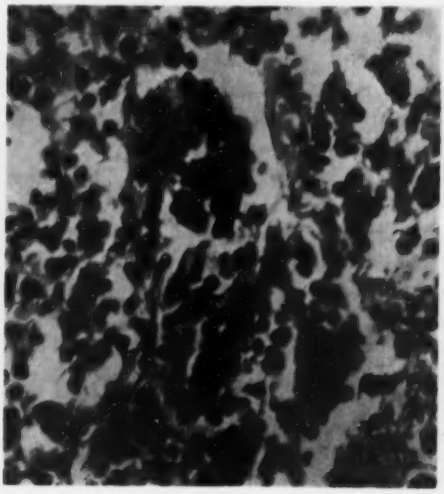


Fig. 8.—Lymph node at autopsy from a case of disseminated lupus erythematosus which shows the intense PAS reaction of the hematoxylin bodies. Periodic acid Schiff reaction; × 500.



or more small, well-defined, PAS-positive granules. These appear to enlarge and either compress and flatten the nucleus against the wall of the cell or incorporate it as a small condensed mass. Rarely, similar oval or round PAS-positive bodies may be seen singularly or in clusters free in the tissue.

In postmortem material many of the plasma cells in the lymph nodes also had a PAS reaction of the cytoplasm which varied from strongly to weakly positive. Intracytoplasmic bodies, similar to those seen in the biopsy material, were identified in the lymph nodes from all autopsies.

Also present in four cases of disseminated lupus at autopsy were typical PAS-positive hematoxylin bodies[7-10] (Fig. 8). Nuclei were still recognizable in some of these structures. Adjacent to, and sometimes a part of, the hematoxylin bodies were cells with PAS-positive inclusions within the cytoplasm.

Material from lymph node biopsies in the remaining cases of "collagen disease" tended to show a similar type of hyperplasia with an increase in plasma cells, which had PAS-positive cytoplasm but no intracytoplasmic inclusions. This increase in plasma cells was marked in two patients. One was a woman who was sensitive to iodine and who had previously had a mastectomy for carcinoma, with active rheumatoid arthritis, and the other was a woman with "collagen disease," type unknown. The lymph nodes of these two patients also disclosed a few plasma cells with cytoplasmic inclusions resembling those seen in lupus. There were six additional instances in which these inclusions were identified: two patients with carcinoma of the lung; one with benign acanthosis nigricans and squamous-cell carcinoma of the scrotum; one with pulmonary fibrosis of unknown etiology, and two who are living and well. None of these patients had recognizable "collagen disease."

Other entities which disclosed numerous plasma cells with PAS-positive cytoplasm but without inclusions could be placed in several groups. Lymph nodes from 10 of 12 patients with skin reactions revealed these cells, as well as the hyperplasia usually associated with diseases of the skin. Another group with this change consisted of patients with malignancy. Here the response was variable, but approximately one-third of the cases had a significant number of PAS-positive plasma cells. The type of tumor was not significant, except that these cells were not seen in the patients with leukemia or lymphoma. There were 17 of 82 cases in the remaining groups listed as "living and well" and "other existing diseases" which had numerous plasma cells with PAS-positive cytoplasm.

Comment

In this study the enlargement of superficial lymph nodes was frequently associated with serious, and often fatal, systemic disease. This was true even after excluding those patients in whom a histopathologic diagnosis characteristic of a specific disease was made. In 158 patients in whom the histopathologic diagnosis of the lymph node was not helpful to the clinician, 26 developed "collagen disease," and 37, malignancy. Forty-seven of the one hundred fifty-eight patients are living and well. Fifty-five patients in this study are dead; their average time of survival was 13 months after biopsy. Therefore, a patient with lymphadenopathy unexplained by biopsy deserves long-term careful observation on the part of the clinician.

In this group of 158 patients the histologic diagnosis based on studies of the lymph nodes usually returned to the clinician was hyperplasia. The criteria for such a diagnosis based on lymph nodes are well defined. Basically, they are an increase in the number and immaturity of the cells; however, the term hyperplasia indicates only the histologic changes present, rather than the diagnosis of a specific disease.

In this study, the designation of hyperplasia has been used when any of the following changes are present, either singly or in combination: (1) an increase in the number or immaturity of cells within the pulp of

the lymph node; (2) more prominent or numerous sinusoidal cells which may or may not be associated with changes in the lymphocytic elements, and (3) follicles in which there are germinal centers containing mitoses or nuclear debris or both. These general categories cover the essential component structures of the lymph node and serve as good indicators of the status of cellular activity.

Occasionally other abnormal cellular findings are associated with hyperplasia. These include numerous or bizarre mitoses outside the follicles; multinucleation, particularly of the sinusoidal or reticuloendothelial cells; increase in size and variability of shape of the nuclei, and marked increase in immature lymphocytes in the pulp of the lymph node. These changes may also occur singly or in combination. It has been the practice at this institution to designate such lesions as "atypical hyperplasia" or "hyperplasia with abnormal cells." With this diagnosis has gone the inference of possible serious disease in the future course of the patient. The material from lymph nodes from 12 patients in our series was originally thought to show "atypical hyperplasia." Seven of these patients developed lymphoma; four, "collagen disease," and one is living and well five years after biopsy.

Since lymphadenopathy occurs frequently, any criteria which characterize a type of hyperplasia as specific would be of help in early diagnosis. These might also aid in the understanding of the disease process.

In hyperplastic lymph nodes, the presence of large numbers of plasma cells with cytoplasm that is PAS-positive appears to be of significance. They are frequently related to diseases which are considered by some to be the result of antigen-antibody reactions.[6,11,12]

The most significant and specific change was present in the material from biopsies of lymph nodes from patients with disseminated lupus erythematosus. This was a PAS-positive inclusion body within the cytoplasm of some of the plasma cells. These structures may be similar to Russell bodies. They are less well defined, less eosinophilic, and frequently much larger than the usual Russell body. However, they may represent a variant of this structure. Mast cells may superficially resemble these altered plasma cells and may have the same tinctorial appearance with the PAS reaction. Differentiation can be made, however, by the use of the metachromatic reaction.

Thus, a great deal of caution must be used in interpreting these inclusion bodies in the plasma cell, since many lymph nodes show PAS-positive material free and within other cells. This is particularly true of the reticuloendothelial components. It is also a distinct possibility that some of the structures described above are in wandering or free reticular cells or immature lymphocytes, since with displacement and compression of the nucleus the type of cell cannot always be identified definitely. Several other entities give rise to numerous plasma cells with diffuse PAS-positivity of the cytoplasm. Hence, the finding of the cells alone cannot be used as an indicator of the disease. Consequently, unless the characteristic PAS-positive inclusion is identified within some of the plasma cells, no suggestion of disseminated lupus erythmatosus should be made.

Hematoxylin bodies in lymph nodes were identified only at autopsy and only in cases of disseminated lupus erythmatosus. The large, irregular hematoxylin bodies appeared to be a mixture of the intracytoplasmic PAS-positive structures and nuclear remnants (Fig. 9). This nuclear material would account for the uptake of hematoxylin. The smaller hematoxylin bodies present in lymph node tissue at autopsy may also represent a mixture of nuclear material and intracytoplasmic inclusions which have been released from the cells. In the absence of nuclear remnants, these PAS-positive structures fail to stain with hematoxylin. The presence of "eosinophilic" hematoxylin bodies in the tissues of patients dying of lupus erythematosus, which do not stain with hematoxylin and

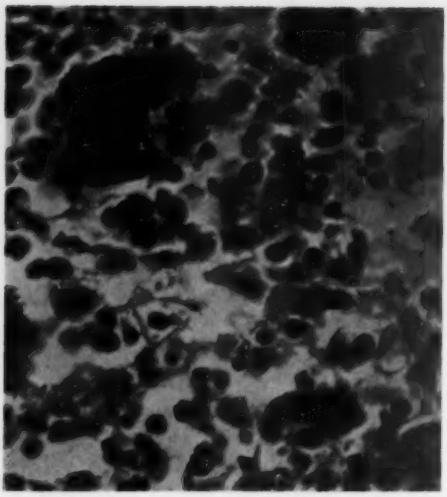


Fig. 9.—Hematoxylin bodies in a lymph node at autopsy from a case of disseminated lupus erythematosus which contain occasional irregular masses and fragments of nuclear material. Hematoxylin and eosin; × 650.

in which the Feulgen reaction is negative, has been pointed out by Gueft and Laufer.[10] They ascribed this to complete disappearance of deoxyribonucleic acid. From our study the absence of nuclear material could be explained by failure of the intracellular inclusions to incorporate such material prior to or after their release from the cell. Furthermore, the hematoxylin body was present only when there was necrosis of lymph node tissue. Necrosis of lymph nodes in lupus erythematosus which has been frequently pointed out in autopsy material[4,5,8,9] was not seen in any of the biopsy material. However, lymph nodes removed from the same patients at autopsy had areas of necrosis, suggesting that the necrosis was a terminal event.

Summary

The clinical and histopathologic diagnoses in 379 patients who had been biopsied because of unexplained, persistently enlarged, superficial lymph nodes were reviewed. In 158 of them the histologic changes were originally characterized as nondiagnostic. The majority were reported as hyperplasia. Many of the patients in this latter group developed recognizable serious illness within a brief period after biopsy, "collagen disease" and malignancy being predominant. Consequently, the clinical course of patients with unexplained regional or generalized lymphadenopathy should be closely followed.

On review, the histology of the lymph nodes was helpful in recognizing the presence of disseminated lupus erythematosus. There was a fairly characteristic hyperplasia in which plasma cells with PAS-positive cytoplasm were prominent. In addition, plasma cells containing cytoplasmic PAS-positive inclusions were found in the lymph nodes in all cases of this disease.

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The Treatment of the Nephrotic Syndrome with Steroids in Children and Adults

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The "nephrotic syndrome" may be defined as a combination of clinical and laboratory findings including massive edema, marked proteinuria, hypoproteinemia, and hyperlipemia. This syndrome may be associated with such diseases as diabetes mellitus (Kimmelstiel-Wilson syndrome), renal amyloidosis, renal vein thrombosis, syphilis, and heavy-metal poisoning. However, in common usage nephrosis or the nephrotic syndrome refers to the so called "pure" or "lipid" nephrosis and to the nephrotic stage of glomerulonephritis. It is possible that the latter two forms are caused by the same basic mechanisms.

Pathogenesis and Pathologic Physiology

We believe that nephrosis is a distinct disease with an immunologic basis and is characterized by a complement-binding antigen-antibody reaction. This antigen-antibody reaction acts to produce functional and, when persistent, morphologic tissue damage. It is probable that not only the glomerular capillary but many of the other capillaries in the body are similarly altered, leading to a generalized increase in glomerular and capillary permeability.

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Mechanism of Edema Formation.—In the glomerular capillary there is increased passage of serum proteins to produce a proteinuria. In the systemic capillaries, which are basically much less permeable, there is an increased filtration rate for water but not necessarily an increased permeability to proteins. Semipermeable collodion membranes can be produced which have approximately the same filtration characteristics as skin capillaries. Only when, by the addition of ether to the collodion membrane, the filtration rate for water is increased more than 26 times does human albumin start to pass through this membrane.[1] The fluid in the chest cavity and the ascites in nephrotics is found to be low in proteins. This increased permeability may also account for the common finding of inulin clearances above normal in the nephrotic syndrome, especially in the early phases of the disease, when loss of complete nephrons has not taken place as yet.

Clinically the edema in the nephrotic syndrome resembles the edema seen in acute allergic reactions, e. g., serum sickness in which the edema is also due to increased capillary permeability. It is highly questionable that the lowered oncotic pressure of the serum is one of the main causes for the edema formation. It may be noted that during the first few days of diuresis in the nephrotic syndrome the oncotic pressure does not change although the edema vanishes rapidly, and, conversely, at the onset of the disease the oncotic pressure may still be well within normal limits while massive edema appears.

The Antigen-Antibody Reaction.—We have reported that serum complement levels

are usually lowered in the nephrotic syndrome,[2] and this finding has been confirmed by others.[3-5] Our most recent compilations indicate that the serum complement level was lowered in 87% of the 369 determinations in 61 cases with the nephrotic syndrome.

The degree of lowering of serum complement (C′) is a function of the size of the antigenic surface involved, provided that ample amounts of antibody are available. It also is a function of the body's ability to form C′. When the antigenic surface is small, as in bacterial diseases, the body is well able to cover the needs of a complement-binding antigen-antibody reaction without a general lowering of the C′ level. When, however, the antigenic surface becomes large, as is the case when the glomerular surface (1 sq. m. in the adult) is involved, the body cannot provide rapidly sufficient amounts of C′ and the serum level falls. That such a surface dependent relation exists has been shown in studies by Seltzer, Baron, and Fusco[6] and by Rice.[7] We were recently able to demonstrate[8] that in experimental nephrosis of the rabbit due to nephrotoxic duck serum lowering of complement is related to the amount of serum injected and to the severity of the resultant disease. Mild forms of the disease can be produced in the rabbit by the use of small amounts of nephrotoxic serum in which C′ does not fall to subnormal levels, while somewhat larger amounts lead to a marked fall of C′ and much more severe disease.

In mild cases of nephrosis or at the beginning or end of the active disease, when the antigenic surface area may be small, the body can cover the needs of complement without lowering the serum C′ level to subnormal values. It has been noted in most of these instances, however, that with the end of the active disease the C′ values

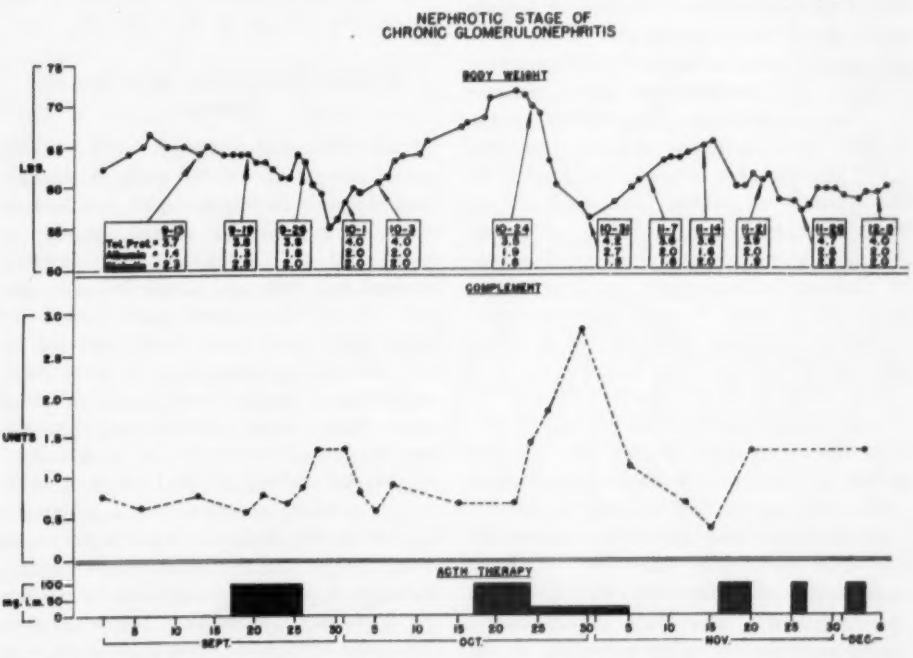

Fig. 1.—Influence of repeated courses of corticotropin (ACTH) therapy on serum complement, diuresis, and plasma proteins in a child with the nephrotic stage of glomerulonephritis. Note high rebound complement values on the 30th day subsequent to corticotropin therapy.

rose appreciably above the values encountered during the active phase. There is probably an increased formation of C′ during the active phase, as suggested by the fact that after the termination of the active disease the C′ values go up to abnormally high values for a few days (rebound phenomenon), only to return to the normal range shortly thereafter. The increased binding of C′ during active disease apparently stimulates increased production (Fig. 1).

The prolonged lowering of C′ level during subacute glomerulonephritis and the active phase of the nephrotic syndrome is difficult to explain. Saturation of the antigen with antibody and use of the C′ could be reasonably expected to end within a short period of time, and the C′ should rise to normal and the immunologic part of the disease subside. It is conceivable that the resultant antigen-antibody complex may again be antigenic, thus leading to a vicious cycle. The splendid studies on the mechanism of antibody-antigen reactions of Najjar and Fisher,[9] using an enzyme as an antigen, would seem to support this thought.

Effect of Corticotropin and Cortisone on Antigen-Antibody Reactions.—Farnsworth [10] first indicated that corticotropin (ACTH) was able to produce a diuresis in the nephrotic syndrome. This gave rise to much speculation as to the mode of action. Attempts to explain the effect on the basis of clearance studies have not been satisfactory.[11,12] While in some instances renal clearances increased with or shortly after the onset of diuresis, they failed to do so in others in spite of an equally effective diuresis. In addition, the fact that such a diuresis does not occur before the 7th and usually after the 10th day of medication makes this explanation still less tenable.

Corticotropin and cortisone suppress the formation of certain antibodies.[13-16] Some observers have disputed this fact.[17] Hanan and Overman [18] have made a most illuminating contribution in showing that in the same rabbit the antibody formation to beef albumin can be completely suppressed by corticotropin, while antibody formation to sheep cells is not influenced. We were able to show [8] that cortisone can completely or partially suppress the antibody formation to duck nephrotoxic sera which cause a nephrotic syndrome in rabbits and that the hormone can thus prevent or interrupt the occurrence or presence of the disease in the rabbit by this mechanism. We have emphasized that in the rabbit only large amounts of cortisone have such an effect (20 mg/kilogram of body weight per day) while smaller amounts (5 mg/kilogram/day) were ineffective. In these experiments it takes about a week before the antibody level is sufficiently reduced to bring the disease into remission. In these animal experiment proteinuria and hematuria can be prevented or markedly decreased by cortisone. Animals given a sufficient amount of nephrotoxic sera developed more or less severe uremia in which a high precentage of them died, while those receiving large amounts of cortisone (20 mg/kilogram/day or more) did not develop uremia or die (Fig. 2).

Steroid Therapy for Induction of Diuresis

Our recommended dosage for the induction of diuresis is 100-200 units of aqueous corticotropin (25-50 units q.6.h.). Children under 40 lb. of body weight usually received 100 units, while heavier children received 160 units and adults 200 units per day. These doses were arrived at after initial trials and errors had convinced us that failures to induce diuresis were more common with smaller doses than with larger doses. More recently we have tended to prolong the initial course of corticotropin therapy beyond the original 10-14 days up to 20 days, especially in cases with a prolonged history of the disease. Diuresis occurs in such cases during the corticotropin therapy, although it is usually more dramatic when the hormone is withdrawn before or with the onset of diuresis. Simultaneously with the hormone therapy the patients received 2-4 gm. of potassium chloride per day and

RABBIT		DAYS -2	0	+1	+6	+6	+7	+8	+9	+10	+11	+12	+13	+14	+15	+33
B 5*	THERAPY		NONE													
	URINE PROT.	–	–	–	3+	AN	4+	4+	4+	4+	D					
	B. U. N. mg%	14		12				80								
B 6	THERAPY		NONE													
	URINE PROT.	–	–	–	–	3+	1+	2+	4+	3+	3+	1+	2+	2+	2+	
	B. U. N. mg%	11			12			53								
C 5	THERAPY		NONE													
	URINE PROT.	–	–	–	–	4+	4+	AN	4+	1+	3+	2+	2+	2+	2+	1+
	B. U. N. mg%	17			15				52						53	32
F 1	THERAPY				60 mg Cort.											
	URINE PROT.	–	–	–	AN	–	–	TR	1+	2+	1+	2+	2+	2+	2+	
	B. U. N. mg%	15									25					
E 4	THERAPY		40 mg Cort.													
	URINE PROT.	–	–	–	–	–	–	2+	2+	2+	2+	2+	2+	2+	3+	
	B. U. N. mg%	16							20						14	
E 8	THERAPY		40 mg Cort.													
	URINE PROT.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1+
	B. U. N. mg%	12								21					14	18
C 11	THERAPY						35 mg Cort.									
	URINE PROT.	–	–	–	–	–	TR	2+	2+	2+	3+	3+	3+	2+	1+	–
	B. U. N. mg%	18							13						21	9
D 1	THERAPY						35 mg Cort.									
	URINE PROT.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	B. U. N. mg%	19			21				15						22	10
D 2	THERAPY						35 mg Cort									
	URINE PROT.	–	–	–	–	–	–	1+	1+	2+	3+	3+	3+	3+	1+	–
	B. U. N. mg%	16			23					21					18	4

All animals received 5ml Anti-rabbit Kidney Duck Serum i.v. on days 0 and 14.

AN=anuria TR=trace D=died *16 additional control animals either early or showed evidence of severe proteinuria starting the fifth day and uremia

Fig. 2. — Proteinuria and BUN in nine rabbits in which nephrotoxic nephritis was produced by intravenous injection of anti-rabbit-kidney duck serum. Six animals received varying amounts of cortisone intramuscularly.

a diet which was slightly restricted in sodium (400-600 mg. per day) but otherwise normal, neither forcing nor withholding protein intake.

With this type of therapy in 42 children and 19 adults massive diuresis was induced in the initial attempt in 82% of our cases (68% in adults, 88% in children). Diuresis to the edema-free state was finally induced in all of the remainder except in one instance, an adult who still is edematous in spite of numerous attempts with different steroids. Some of the resistant patients required as many as five attempts until a full diuresis was induced. If the first attempt failed, the dose of corticotropin was increased in steps of 40 units per day in each course. More recently we have achieved good results in these resistant cases by extending the initial therapy up to 20 consecutive days, as suggested by Greenman, Weigand, and Danowski.[19] The resistant group consisted mostly of cases who had had a prolonged course of disease with evidence of advanced morphologic glomerular damage as shown by an elevated blood pressure, many granular casts in the urine, and often a prolonged rise in NPN. It should be emphasized, however, that such signs should only serve to intensify hormone therapy rather than to abstain from it. Several of these children and adults with marked nephritic features in addition to their nephrotic syndrome diuresed on therapy only after several attempts. On subsequent maintenance therapy they returned slowly to normal blood chemistry values but were left with a residual mild proteinuria. When massive edema was present filling the chest cavities and the abdomen with large amounts of fluid, small paracenteses were occasionally performed to prevent respiratory and circulatory embarassment.

With corticotropin and cortisone the onset of diuresis has been accompanied or preceded by 24 to 48 hours by a rise in C′ to or toward normal values. The rise in C′ often preceded a decrease in proteinuria (Figs. 1 and 3) or a rise in the oncotic pressure of the plasma as measured by the Hepp osmometer.[20] This rise in C′ is considered the expression of a decreasing antigen-antibody reaction due to a depressed antibody formation. When C′ does not rise, diuresis does not occur. Temporary diuresis induced by raising the oncotic pressure of the plasma with dextran infusions

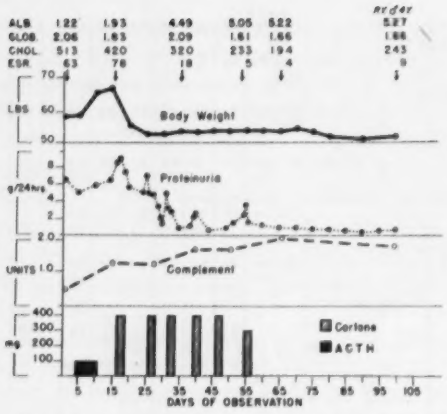

Fig. 3.—Complement, body weight, and proteinuria in a child with a nephrotic syndrome given corticotropin (ACTH) and intermittent cortisone (Cortone) therapy.

does not lead to a rise in C′, as shown by Barnett.[21]

Without further therapy after the initial induction of diuresis most cases relapsed or recurred within one year (69% of 52 cases). Fifty per cent of the cases relapsed within six months. These results are in general agreement with those of others.[22] Relapses can occur within a few days after discontinuation of therapy, and C′ falls rapidly to subnormal levels. It is suggested that there is a rapid resumption of antibody formation once the checkreins of the steroids on antibody formation are removed.

Another type, which we like to call recurrence rather than relapse, occurs when after a prolonged edema-free period reaccumulation of edema occurs within two to three days after an infectious disease, e. g., upper respiratory disease, tonsillitis, varicella, mumps, pneumonia, or measles. The rapidity of the recurrence suggests an anamnestic reaction. In two instances, there was recurrence after a second injection of γ-globulin, and in one[23] it occurred within two days after an injection of Salk vaccine. Whether immunization procedures may be hazardous in persons in remission from a nephrotic syndrome should be studied further.

Mechlorethamine hydrochloride (nitrogen mustard) given to adults with the nephrotic syndrome caused a diuresis in five instances with a serum complement behavior identical with the one seen before and after spontaneous diuresis or diuresis induced by corticotropin or cortisone. When corticotropin, cortisone, or mechlorethamine hydrochloride was administered in similar amounts to normal persons or persons suffering from conditions other than nephritis or nephrosis, C′ did not change.[24,25]

When relapses or recurrences occurred after corticotropin or cortisone therapy, serum complement usually fell to subnormal levels one to four days prior to the appearance of overt edema, although in some instances with a slow onset of the recurrence C′ fell only after edema had already set in.

Initial diuresis can be induced by cortisone, giving doses of 300-400 mg. per day for 10-14 days (Fig. 4). This therapy was successfully carried out in eight instances. At the end of therapy one to two injections of 25 units of corticotropin are given to prevent a period of adrenal insufficiency after suppression of the adrenals by the massive cortisone medication. Where such corticotropin medication has been omitted, an Addison-like syndrome can appear within 24 hours after the discontinuation of the cortisone.

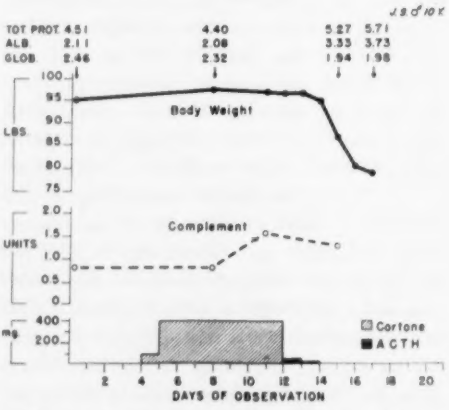

Fig. 4.—Complement, body weight, and plasma proteins in a child with the nephrotic syndrome given oral cortisone (Cortone) therapy.

	CONTROLS					STEROIDS WHEN EDEMATOUS					
	PATIENTS					PATIENTS					
Period (mos.)	At Start	Entered	Died	Withdrew	Death Rate %	At Start	Entered	Died	Withdrew	Death Rate %	Deaths Expected
0-5	35 64 99	0	0 1 1	3 0 3	1.2		60	2	6	3.5	0.68
6-11	32 63 95	0	2 2 4	5 20 25	4.9	52	16	5	7	8.8	2.77
12-17	25 41 66	0	2 3 5	7 5 12	8.4	56	9	5	5	8.6	4.54
18-23	16 33 49	0	0 2 2	2 4 6	4.4	55	3	4	7	7.5	2.51
24-29	14 27 41	0	1 2 3	0 2 2	7.5	47	2	5	6	1.1	3.37
30-35	13 23 36	0	0 1 1	2 2 4	2.9	36	3	5	5	1.4	1.07
36-41	11 20 31	0	0 1 1	1 2 3	3.4	31	1	2	4	7.1	1.00
42-47	9 18 27	0	0 1 1	0 0 0	3.7	26	0	0	5	0	0.87
48-53	9 17 26	0	0 0 0	2 0 2	0	21	0	1	3	5.0	0.00
54-59	7 17 24	0	0 0 0	0 3 3	0	17	0	0	4	0	0.00
60-65	7 14 21	0	0 0 0	2 2 4	0	13	1	1	4	8.3	0.00
TOTALS			18					30			16.81

Fig. 5.—Therapeutic results in patients with the nephrotic syndrome. Data from group with "no steroid therapy" compared to group given "steroid therapy only when edematous." Lower figures in controls taken from Riley.[26]

Repetition of Steroid Therapy Only When Edema Recurs

When relapses or recurrences occur, corticotropin therapy can be reinstituted upon the appearance of edema. Diuresis occurred in the majority of 60 such instances, although less promptly than in the first attempt (63%). Before the introduction of maintenance therapy (i. e., steroid therapy regularly also when edema is absent), some patients had as many as five successful diureses induced by steroid medication each time when they became edematous.

In order to see whether or not such therapy is beneficial as far as mortality is concerned, Riley [26] has suggested that statistical analysis be used according to the life-table method. Our group of cases treated with steroids only when edematous was compared to a group of control cases with the nephrotic syndrome not treated with steroids at all but treated after 1946, so that it can be

	CONTROLS					MAINTENANCE					
	PATIENTS					PATIENTS					
Period (mos.)	At Start	Entered	Died	Withdrew	Death Rate %	At Start	Entered	Died	Withdrew	Death Rate %	Deaths Expected
0- 5	46 112 160		1 2 3	9 0 9	1.9		14	0	0	0.0	0.27
6-11	38 110 148	0 14 14	4 7 9	4 26 30	6.4	14	2	0	0	0.0	1.02
12-17	30 93 123	0 4 4	4 6 10	2 10 12	8.4	16	0	0	5	0.0	1.13
18-23	24 81 105	0 2 2	0 6 6	3 9 12	6.0	11	3	0	3	0.0	0.66
24-29	21 68 89	0 2 2	2 6 8	1 7 8	9.3	11	1	0	2	0.0	0.93
30-35	18 57 75	0 2 2	0 6 9	3 5 8	12.6	10	2	0	4	0.0	1.13
36-41	15 48 63	0 1 1	1 2 3	1 6 7	5.0	8	0	0	2	0.0	0.35
42-47	13 41 54	0 0 0	0 1 1	1 4 5	1.9	6	0	1	3	22.2	0.09
48-53	12 36 48	0 0 0	0 1 1	3 2 5	2.2	2	1	0	1	0.0	0.04
54-59	9 33 42	0 0 0	0 0 0	0 7 7	0.0	2	0	0	1	0.0	0.00
60-65	9 26 35	0 0 0	0 1 1	2 5 7	3.2	1	0	0	1	0.0	0.02
TOTALS			51					1			5.64

Fig. 6.—Therapeutic results in patients with the nephrotic syndrome. Pooled data from group with "no steroid therapy" and "steroid therapy only when edematous" compared to group given "prolonged intermittent steroid therapy." Lower figures in controls taken from Riley.[26]

assumed that sufficient amounts of antibiotics were used (Fig. 5). To the control cases with the nephrotic syndrome treated in our institutions we added, with the permission of Dr. Riley, his control cases, also not treated with steroids, to make the control sample larger and the distribution more even. Dr. Riley's values are noted in the lower figures of each group in Figures 5 and 6. The observations were divided into six-month periods after onset of the disease of each person. The distribution between adults and children was approximately 1:2 in our material, while Dr. Riley's cases consisted of children only. The term "withdrew" in the statistics (Figs. 5 and 6) comprises persons lost to follow-up and those who were transferred to another group, e. g., to steroid therapy when edematous or to maintenance therapy. The death rate was calculated according to the formula.

$$\frac{\text{Died}}{\text{No. at start of period} + \tfrac{1}{2}\left(\text{No. entering during interval}\right) - \tfrac{1}{2}\left(\text{No. during interval withdrawing}\right)}$$

From the Figures it becomes evident that the peak in mortality is in the second year of the disease, with a slightly lower death rate in the third year and a marked decline in mortality thereafter. In the control group of 99 cases observed for 65 months after onset of the disease the over-all mortality was 36.4%. To our great surprise the group given steroids only when edematous (Figs. 5 and 7) did not only not show any decrease in mortality compared to the "control group" but had a statistically significant ($P<0.01$) increase in mortality. In this group 51.3% of the cases were dead after 65 months. We are inclined to believe that the reason for this result lies in the fact that the severer cases were treated with steroids, while those who seemed initially to have a better prognosis were left untreated.

Maintenance Therapy

We have explored methods to depress antibody formation for prolonged periods. When corticotropin (25 units/day) was given to two children continuously they relapsed during therapy with a fall in complement and reaccumulation of edema. The continuous use of large doses of steroids, however, was impossible due to the well-known side-effects of such medication. After much trial and error, which we have described previously,[27,28] a scheme of medication for maintenance therapy, that means steroid therapy regularly also when edema is completely absent, was worked out which combined doses large enough to prevent relapses or recurrences with the avoidance of Cushing-like symptoms. When a successful and complete diuresis was induced by the method described above, every patient, since 1951, was started on cortisone maintenance therapy five days after the onset of the diuresis. In cases where the corticotropin therapy was continued beyond the onset

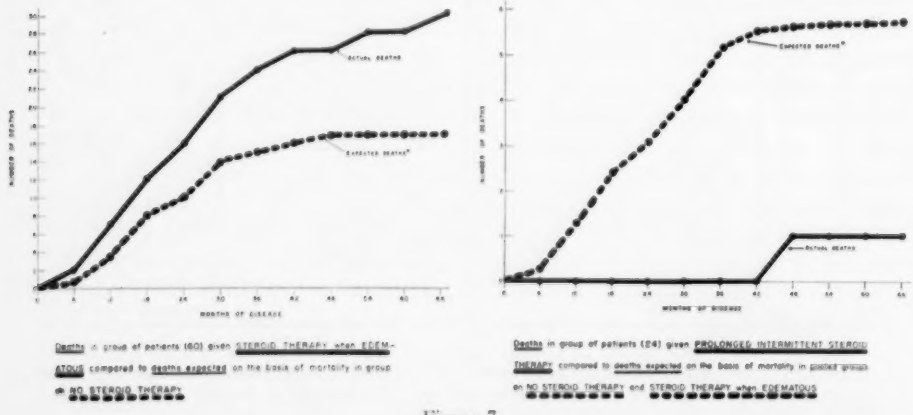
ACTUAL DEATHS
EXPECTED DEATHS*
NUMBER OF DEATHS
MONTHS OF DISEASE
Deaths in group of patients (60) given STEROID THERAPY when EDEMATOUS compared to deaths expected on the basis of mortality in group on NO STEROID THERAPY.
EXPECTED DEATHS*
ACTUAL DEATHS
NUMBER OF DEATHS
MONTHS OF DISEASE
Deaths in group of patients (24) given PROLONGED INTERMITTENT STEROID THERAPY compared to deaths expected on the basis of mortality in pooled groups on NO STEROID THERAPY and STEROID THERAPY when EDEMATOUS

Figure 7

of diuresis, cortisone maintenance was started five days after the termination of the corticotropin therapy. Maintenance consisted of oral cortisone, 300 mg. per day in three divided doses to children under 40 lb. of weight and 400 mg. in four divided doses per day to all others, children and adults alike.* These doses were given for three successive days of each week, e. g., Mondays, Tuesdays, and Wednesdays. This maintenance therapy was continued for at least one year and then tapered off by prolonging the intervals between courses rather than decreasing the cortisone doses. After an additional two months of this diminished therapy maintenance has been discontinued. Twenty-four persons (nineteen children and five adults) were treated with this form of maintenance therapy. They were observed after discontinuation for a period of from one to five and one-half years. The average time of observation was 41.5 months after start of maintenance therapy. These cases were hospitalized usually for only the period of the initial corticotropin therapy and one course of maintenance therapy. Thereafter they were followed on an outpatient basis. The results of this therapy are shown in Figures 6 and 8. As suggested by Riley,[26] it appeared advisable to compare the results of this group with the pooled results of the groups receiving no steroid therapy and steroid therapy only when edematous. From the results of this 65-month observation of this relatively small but unselected group it appears that with this type of therapy mortality within this period was reduced from an expected number of 5.64 deaths to 1. This result is significant with a probability level of 95%. An additional 12 cases (8 children and 4 adults) were similarly treated, but they are not 12 months after the end of maintenance therapy as yet and were therefore not included in the statistics. All cases of the group of 12 not included in the statistics are alive and free of edema. We have not seen a relapse or recurrence while given maintenance therapy; however, we have seen recurrences after discontinuation of therapy, usually produced by infectious diseases when the maintenance therapy was discontinued after less than a year. No recurrences were seen so far when maintenance therapy was continued for at least one year.*

We have attempted to induce diuresis in two cases with maintenance therapy from the start. Both attempts have failed. Three similar unsuccessful attempts by others have come to our attention. In our own cases diuresis was subsequently induced by a full course of corticotropin treatment for 14 days, and this was followed by cortisone maintenance therapy for 1 year. Both cases are free of edema or chemical abnormalities two and five years after the end of therapy, respectively.

We are well aware that the group on maintenance therapy is small and that the comparison to the much larger control group is statistically not ideal. On the other hand, when the maintenance group is compared to the smaller control group of our own observation in Figure 6, the result is almost identical with the result obtained from the comparison with the larger control group.

With this type of maintenance therapy the abnormalities in blood chemistry usually return rapidly to normal. By the end of the fifth week of maintenance therapy plasma proteins, cholesterol, and BUN had returned to normal in 23 of the 24. One still has an elevated cholesterol level and a 3+ proteinuria. By the end of maintenance therapy proteinuria had diminished to 0 in 14 cases (61%), 1+ in 6 cases (26%), 2+ in 2 cases (9%), and 3+ in 1 case (4%). None

* Drs. S. Fromer, E. Alpert, and F. K. Heath, of Merck & Co., Inc., supplied us with liberal amounts of cortisone.

* During the past 18 months we have substituted in a number of cases prednisone and prednisolone for cortisone in a ratio of 1 mg. of these drugs for each 4 mg. of cortisone given otherwise. These drugs seem to maintain the edema free state just as well as cortisone; but in the doses given there was no decrease in sodium retention as compared to cortisone and we had the impression that Cushing-like signs appeared more readily.

of these levels has increased since, except temporarily during febrile diseases.

The average hospitalization of cases not treated with prolonged intermittent therapy and not dying during the first year was 57.5 days per year of observation. Cases given prolonged intermittent therapy have been hospitalized only until diuresis was completed and for the first maintenance course. Thereafter they have been treated at home.

All children given intermittent maintenance therapy were subjected to bone X-ray survey every six months. No abnormalities in bone development have been observed thus far. Comparison with standard growth tables indicated that growth and development of these children apparently have remained within normal limits during and after maintenance therapy. In children with continuous steroid therapy Sobel [29] has noted marked developmental disturbances.

There was no basic difference in the clinical behavior of adults and of children with the nephrotic syndrome. Both responded to the same therapeutic regimen. It was noticeable, however, that the residual damage after the end of therapy was usually more pronounced in the adult group than in the children's group, leaving them frequently with residual proteinuria. It has been observed that those patients (adults and children) who have been treated early in their disease (within one month after onset) with this intensive therapeutic regimen had a much better result than those who were not treated until they had had several episodes of the nephrotic syndrome or after one episode lasting for more than three months of the disease. Of the early cases 83% had no proteinuria at the end of observation, while of the cases in whom the disease existed much longer and often with several episodes of remissions and relapses only 28% are completely free of proteinuria. The presence or absence of proteinuria, however, can not be made the criterion of healing. Patients may be left with a residual proteinuria (healing with defect) and go on to a normal life, as is proved by a number of adults who are known to have had "nephrosis" as children, had "spontaneous remissions," and are discovered after many years to have a constant mild proteinuria.

Recommendations for Therapy

Prolonged intermittent maintenance therapy with large doses of cortisone has apparently reduced mortality to a considerable extent in a five-year observation. Whether or not this represents a permanent cure remains to be seen. From these observations certain recommendations can be made as to therapy.

Diuresis can be induced with corticotropin (100-200 units per day) given for 10-20 days, depending on the severity and duration of the disease. Antibiotics are given during the course. When the first therapeutic attempt does not induce diuresis a second course with a larger dose and for a longer period should be attempted after a short interval.

Five days after the onset of diuresis—but only when diuresis occurs—oral cortisone (300 mg. per day to children under 40 lb.; 400 mg. per day to all others) is given on three successive days of each week. Maintenance therapy with cortisone should not be started unless complete diuresis has occurred. Maintenance therapy can not induce diuresis, and no such attempts should be made, since they tend to delay proper therapy. Oral antibiotics and potassium chloride (1-2 gm.) may be given during maintenance therapy. The doses of cortisone used should not be reduced, since, with smaller doses, relapses occur occasionally. The interval between courses should not be extended during the first year of therapy. After one year therapy is gradually terminated by prolonging intervals between maintenance courses rather than by decreasing the dose.

The favorable results obtained with this therapy so far appear to be a good lead,

although no definite proof that the active disease can be arrested by massive prolonged steroid therapy. The final outcome, especially as to life expectancy after such therapy, will require much longer observation.

Summary

The nephrotic syndrome as discussed in this paper is defined as the result of an antigen-antibody reaction in which large amounts of complement are used. It comprises the forms formerly called "lipid nephrosis" and the nephrotic stage of subacute glomerulonephritis but no other forms of nephrosis.

The pathogenetic mechanism leads to an increased capillary permeability in the glomeruli and probably throughout the body.

Serum complement levels were low in 87% of 61 cases with the nephrotic syndrome.

Serum complement levels can be normal in very mild cases or in the beginning or at the end of the disease.

Corticotropin and cortisone depress the formation of certain antibodies. They do so in the experimental nephrotic syndrome induced in the rabbit by nephrotoxic duck sera. They prevent or markedly ameliorate this experimental disease when given in large amounts.

In 82% of children (42 cases) and 68% of adults (19 cases) complete diuresis was induced in the first attempt with large doses of corticotropin. All except one case could be completely diuresed when repeated attempts were made in case of initial failure.

Diuresis is always preceded by a rise in complement. When complement does not rise, diuresis does not occur.

When not further treated after the initial induction of diuresis, 50% of the cases recurred within 6 months and 69% within 12 months.

Corticotropin and cortisone given only when the patients were edematous did not reduce mortality.

When cortisone in large doses was given on three successive days of each week for one year subsequent to the initial diuresis, the mortality of 24 cases observed up to 66 months, with an average length of observation of 41.5 months, was reduced from the expected 5.64 deaths to 1 death. In 12 additional cases observed for shorter periods of time, no death has occurred.

Proteinuria is usually rapidly reduced in cases on maintenance therapy, and blood chemistry values return speedily to normal. By the end of maintenance therapy 61% of the cases were free of proteinuria and have remained so.

Growth and development is not impaired by this prolonged intermittent steroid therapy.

Children and adults with the nephrotic syndrome react equally well to this therapy.

Therapy should be started as early as possible in the disease, since the therapeutic results are then decidedly better.

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Progress in Internal Medicine

Cause of Death in Ruptured Intracranial Aneurysms

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Introduction

The study of intracranial aneurysms has come a long way in the 33 years since Sir Charles Symonds brought together our knowledge of the subject in 1923.[1,2] The relationship between subarachnoid hemorrhage and rupture of aneurysms has been established,[3-6] statistics have been gathered on the frequency of aneurysms on various parts of the circle of Willis and arterial supply of the brain,[7] diagnostic procedures are well worked out,[8-10] the efficacy of various surgical treatments are being compared,[11-15] and the relative value of surgical versus conservative therapy is being determined, although the latter point is by no means settled.[16-22] Clinical syndromes associated with aneurysms in various locations are being elucidated, as far as this is possible.[23,24,36]

However, there are relatively few studies on the actual consequences of the rupture of the aneurysm in fatal cases. Recently Robertson[26] has reviewed the pathologic findings in 97 ruptured aneurysms, 12 of which are reported in some detail. As he pointed out, "The usual conception of aneurysmal rupture is that of an effusion of blood into the subarachnoid space." Yet, of his 97 cases, 58 showed massive intracerebral hemorrhage, 7 reached the ventricular system, and an additional 9 displayed superficial cerebral damage. Three ischemic infarcts were noted, leaving subarachnoid hemorrhage alone the only finding in the remaining twenty.

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Analysis of Cases in Present Series

During the 21-year period from July, 1934, to July, 1955, a diagnosis of proven or possible subarachnoid hemorrhage was made 713 times at the University Hospital. During this same period a proven or tentative diagnosis of intracranial aneurysm or aneurysm of the circle of Willis was made in 243 patients. Seventy-seven of these died while in the hospital. Fifty-nine postmortem examinations were done at which intracranial aneurysms were found or were expected to have been found by antemortem diagnosis. Not all of these were part of the group of 77.

Of the 59 cases there was no definite aneurysm found in 8, and 6 died from other causes (in some the aneurysm, unruptured, was an incidental finding) than rupture of the aneurysm.

Of the remaining 45 cases in which a definite rupture aneurysm was seen, 5 were felt to be distinctly postoperative deaths with no massive bleeding or infarction due to the aneurysm, 4 were thought to have died as a result of anemic cerebral infarction in association with the aneurysm (usually with pneumonia also), and 1 patient definitely died from pneumonia alone.

This leaves, over a period of 21 years, 35 autopsied cases in which death was thought to be due primarily to rupture of an intracranial aneurysm (although operations were performed in some and may have been a secondary cause of death). In culling our cases like this we have attempted to be as honest as possible in assigning the cause of death, but this is sometimes difficult when working from records of which we might not have personal knowledge.

(Most of the cases and autopsy material prior to 1950 has been taken entirely from the records.)

Report of Cases

The 35 cases have been divided into five groups as to the artery of origin of the aneurysm. There were 14 of the anterior cerebral artery or the anterior communicating artery, six of the internal carotid, six of the middle cerebral, four of the posterior communicating or posterior cerebral, and five of the basilar or vertebral arteries. Thus 26 originated from the carotid portion of the circle of Willis, and nine from the basilar part. This is close to the usual ratio.[7]

Anterior Cerebral and Anterior Communicating Group: Fourteen Cases

CASE 1.—A 35-year-old white man was well until the early morning of May 27, 1954, when he noted a severe headache, nausea, and vomiting. He was admitted the next day. Neurologic examination showed a positive Babinski reflex on the right and a stiff neck.

Lumbar puncture showed a pressure of 170 mm. arteriograms were normal, as was a left vertebral of grossly bloody fluid. Right and left carotid arteriogram. Nineteen days after admission the patient suddenly complained of severe headache associated with numbness in the right leg and then in both legs. He died two days later.

Fig. 1 (Case 1).—Ruptured aneurysm of the anterior communicating artery near its junction with the right anterior cerebral artery.

At autopsy there was marked congestion and edema, with blood under the base of the brain and filling all ventricles. There was a small aneurysm of the anterior communication artery (Fig. 1), which had ruptured forming a large blood clot involving both frontal lobes and the caudate nuclei and internal capsules bilaterally. This had ruptured into the ventricles. There was a marked cerebellar pressure cone.

CASE 2.—A 43-year-old white man was well until 10 days before admission, when he complained of pain in the neck. The next morning he awoke feeling nauseated and vomited. He gradually became comatose and was admitted on Dec. 5, 1938. On examination there was early papilledema and a right hemiparesis. Lumbar puncture showed xanthochromia, with a pressure of 200 mm. of water. Repeated lumbar punctures were done. During his first few days in the hospital the patient gradually improved. However, 15 days after admission his condition worsened, and he died 8 days later.

On the basilar vessels of the brain there were several aneurysms, one about 3 mm.×1 cm. on the posterior part of the basilar artery. There were also two aneurysms 3 to 4 mm. in diameter on the anterior communicating artery. There was hemorrhage over the entire left frontal region and extensive recent hemorrhage into the dorsal-medial surface of the right frontal lobe measuring, 2.5×3×3 cm., which undermined the right caudate nucleus and destroyed white matter of the right orbital gyrus. In the left insula there was an extensive area of softening which destroyed practically the entire gray matter of this region. There were a few blood clots in the right lateral ventricle.

CASE 3.—A 14-year-old white boy was well until two months before admission, when he noted a dull pain above the left eye followed within a few minutes by collapse and convulsions. He later had three similar episodes. On the day of admission, July 27, 1942, the patient had another generalized convulsion which was followed by unconsciousness.

On examination he was profoundly comatose. The left eye was more prominent than the right. The pupils were constricted.

A ventriculogram demonstrated a right midbrain mass with marked extension bilaterally into the ventricles. The patient's course was downhill, and respirations ceased 28 days after admission.

At autopsy a slight fullness anterior to the optic chiasm on the left was found. Frontal sections showed marked recent hemorrhage in

the frontal poles which had ruptured into the ventricles. On the anterior communicating artery there was an aneurysm 8 mm. diameter nearly filled with a laminated thrombus. Subarachnoid bleeding was slight.

CASE 4.—A 35-year-old white man had left-sided headaches behind the eye beginning four years before admission. Seven days before admission he was found vomiting in his car. At another hospital lumbar punctures showed bloody fluid. He was admitted on May 27, 1948.

On examination he was semicomatose, and bilateral papilledema was noted which was more pronounced on the right. There was a right facial weakness, and there were pathologic pyramidal tract signs bilaterally. Lumbar puncture showed grossly bloody spinal fluid. With repeated punctures the fluid gradually cleared. The patient's course was uneven.

At operation five weeks after admission there was an organized clot around the optic nerves and anterior cerebral arteries. There were two anomalous vessels from the right and left sides which entered an aneurysmal sac, which was thought to represent an anomalous anterior communicating artery. These vessels were clipped. The sac ruptured, and it was necessary to clip both anterior cerebral arteries as well. The patient died 15 days after the operation.

At autopsy there was a moderate-sized hematoma over the surface of the brain in the operative region. Two metal clips had been attached to the anterior cerebral arteries below the optic chiasm. The thrombosed aneurysm measured 1×0.5 cm. There was extensive hemorrhage which destroyed the anterior two-thirds of the corpus callosum and filled both lateral ventricles. There was necrosis of the midportion of one-half of the frontal lobes anterior from the optic chiasm. There was an enormous hemorrhage involving the genu and rostrum of the corpus callosum, extending posteriorly and reaching just anterior to the splenium of the corpus callosum. The fornix, hypothalamus, and floor of the third ventricle extending to the region of the mammillary bodies were softened.

CASE 5.—A 49-year-old white woman was well until two years before admission, when her headaches became more severe. Two weeks before admission the patient noted severe headaches and nausea. This was followed by lethargy, right hemiparesis, and aphasia.

On admission, on May 22, 1950, examination showed lethargy with complete expressive aphasia. There was bilateral papilledema and a right hemiparesis. The second day after admission the patient was moaning and breathing heavily, and she died shortly thereafter.

At autopsy, there was recent and old subarachnoid and subdural blood over the left hemisphere and at the base of the brain. There was an aneurysm of the anterior communicating artery 1.5 cm. in diameter. There was no gross bleeding into the brain or ventricles. There was a moderate cerebellar pressure cone.

CASE 6.—A 49-year-old white man was in fair health except for frontal headaches until the night before admission, when he was found having convulsions on the floor. He awoke and was confused and complained of headache and neck pain. He entered here on Jan. 30, 1951.

On examination he was slightly confused. There was early papilledema and a stiff neck. The day after admission a lumbar puncture showed a normal pressure with bloody fluid. Seven days after admission the patient had a recurrence of bleeding. One month later the patient suddenly yelled and stiffened out. He became unconscious. The next day a right carotid arteriogram showed an aneurysm at the base of the right anterior cerebral artery. At operation an aneurysm of the anterior communicating artery was seen. The right anterior cerebral artery was clipped below the anterior communicating artery, and the aneurysm sac was clipped on each side. The patient did not improve after this and died six days after operation.

Autopsy showed recent hemorrhage near the operative defect. There was a subdural hemorrhage over the left parietal area. An aneurysm 1.5 cm. in diameter arose from the anterior communicating artery and was adherent to both anterior cerebral arteries. There was an aberrant artery leading from the anterior communicating artery to the left frontal lobe. The right anterior cerebral artery had been closed with a silver clip. The left hemisphere was slightly larger than the right, and its surface was hemorrhagic and necrotic. Lateral to the left internal carotid artery a small hemorrhagic area led into a large area of hemorrhage measuring 5×3×2 cm., which lay below the left lateral ventricle and at one small point entered the ventricle. There was some bloody fluid in the left lateral ventricle.

CASE 7.—A 40-year-old white woman had known hypertension for 15 to 20 years prior to admission. For three to four months before admission she had frontal headaches. The night before admission she was found semicomatose.

Examination on admission, on Sept. 7, 1950, showed a blood pressure of 250/100. She was drowsy, had a stiff neck, and did not voluntarily move her left side. Shortly after admission the patient developed Cheyne-Stokes respirations with cyanosis and died.

On examination of the blood vessels at the base of the brain there was duplication of the vessels, with as many as four small vessels replacing the usual one. Near the junction of the left anterior cerebral and the anterior communicating artery there was an aneurysm of the

anterior communicating artery the size of a large pea. There was hemorrhage extending over the surface of the left hemisphere and over the base of the frontal lobes. There was an area of extreme softening beneath the lamina terminalis, with rupture into the third ventricle and extensive hemorrhage into the ventricular system. The fourth ventricle was greatly distended with a blood clot. There was softening of the basilar portions of the brain.

CASE 8.—A 32-year-old white woman entered the Neuropsychiatric Institute on Jan. 27, 1954, with complaints of dizziness, left frontal headache associated with weakness of the left arm and leg, and difficulty in walking. She was anxious and uneasy with people.

Neurologic examination upon admission was completely normal. While the patient was in the hospital she complained of symptoms of fear, tenseness, and tiredness, accompanied by tremors, excessive perspiration, palpitation, and dizziness. Three months after admission the patient was found unconscious one evening. A lumbar puncture showed a pressure of 350 mm. of water. The fluid was bloody and xanthochromic. One hour later respirations ceased.

Autopsy showed a berry aneurysm at the junction of the left anterior cerebral artery and the anterior communicating artery. This had ruptured into the left frontal lobe, dissected the white substance, and reached the left lateral ventricle. All the ventricles were filled with blood, and the fourth ventricle was somewhat enlarged. There were moderate temporal and marked cerebellar pressure cones bilaterally.

CASE 9.—A 65-year-old white man was well except for occasional headache until seven days before admission, when he noted a sudden intense pain at the base of his skull. He was hospitalized elsewhere and in the next few days had several convulsions and lost partial control of his arms and legs. He was admitted on March 18, 1955.

On examination he was deeply comatose, and the optic disc margins were blurred bilaterally. There was a right lower facial weakness, and the tongue deviated to the right. There were bilateral Hoffman and Babinski reflexes. Lumbar puncture showed a pressure of 320 mm. of xanthochromic fluid. He died the morning after admission.

At autopsy the entire brain was covered with subarachnoid blood. Three aneurysms were seen. From one on the left anterior cerebral artery originated a 3×3 cm. area of hemorrhage in the left frontal lobe which broke into the ventricular system (Fig. 2), filling all the ventricles. There was also a 1.5×1 cm. thrombosed aneurysm of a branch of the left middle cerebral artery in the third left frontal convolution. There was in addition a small aneurysm of the anterior communicating artery. A blood clot was seen coming through the roof of the third ventricle and causing softening of the surrounding areas. There were bilateral cerebellar pressure cones.

Fig. 2 (Case 9).—Ruptured aneurysm of the left anterior cerebral artery, with subarachnoid, intracerebral, and intraventricular hemorrhage.

CASE 10.—A 58-year-old white man was well until five years before admission, when he had a sudden loss of consciousness for which he was bedridden for four months. Recovery was only partial, and personality changes persisted and were progressive. During the year prior to admission the patient had weakness, memory loss, and personality change. He entered on Sept. 18, 1941.

Examination showed a poor memory and some disorientation. Blood examination showed a hemoglobin value of 25% with a red cell count of 1,160,000; white cell count was 3100. A diagnosis of pernicious anemia was made, and he was given blood transfusions. Ten days after admission he awakened complaining of headache. Two hours later he had a tonic convulsive movement and subsequent flaccidity. The eye grounds showed extensive and spreading subhyaloid hemorrhage in both discs, with early papilledema. There were bilateral Babinski reflexes. Lumbar puncture showed a pressure of 550 mm. of bloody spinal fluid. Seven hours later the patient died.

Autopsy showed the base of the brain to have been largely destroyed by massive hemorrhage. In the base of the frontal lobe in the midline there was an aneurysm which measured 6×5×5 cm. and which originated from the right anterior cerebral artery. The left anterior cerebral artery could not be identified, and the anterior communicating artery was thinned out. The aneurysm had ruptured into the base of the left frontal lobe, forming a blood clot 6×6×2 cm., and from there into the subarachnoid spaces

and cisterns and had broken into the entire ventricular system, apparently starting from the left anterior horn. The hemorrhage had destroyed the septum pellucidum, the fornix, the quadrigeminal region of the midbrain, the cerebral and cerebellar peduncles, the pineal gland, and the basal ganglia.

CASE 11.—A 48-year-old white man was well until two and one-half years before admission, when he had an episode of headache, chills, stiff neck, and unconsciousness which lasted for three weeks. The morning of admission, April 29, 1944, he suddenly complained of severe headache and vomited. Examination showed a patient who was stuporous but could be roused. There was an alternating divergent strabismus and slight right facial weakness. There were bilateral Babinski reflexes present. Lumbar puncture showed a pressure of 250 mm. of bloody and xanthochromic fluid. Three days after admission the patient was confused and soon became comatose. He died eight days after admission.

Autopsy showed subarachnoid hemorrhage extending from the mid pontine region inferiorly over the brain stem and out around the cerebellum. There was a 1.2 cm. aneurysm of the left anterior cerebral artery which probably had ruptured into the left lateral ventricle. Blood filled the lateral ventricles, third ventricle, aqueduct, and dilated fourth ventricle.

CASE 12.—A 48-year-old white man had had recurrent headaches for three years and high blood pressure for one year prior to admission. Eleven days before admission he awoke with an intense occipital and frontal headache, vomited, and was incontinent of urine. He was taken to a hospital elsewhere, where a lumbar puncture showed bloody fluid under increased pressure. He entered here on Sept. 18, 1947.

Examination showed a stuporous man whose mind appeared to wander. There was elevation of the disc margins and a questionably positive Babinski reflex bilaterally. There were forced grasping movements with both hands. During a seizure both sides of the body were involved, beginning with the right arm. The head turned slightly to the right. Following the seizure he was found to be areflexic on the left side and soon became comatose. The same day a right ventriculogram showed a shift of the ventricular system to the right. The fluid removed was grossly bloody. Following this, a left frontal osteoplastic craniotomy was done. A biopsy of the brain revealed encephalomalacia. Postoperatively the patient never regained consciousness, and respirations ceased the next morning.

Autopsy showed an aneurysm 5 mm. in diameter of the left anterior cerebral artery, close to the origin of the anterior communicating artery. Hemorrhage extended anteriorly along the inferior aspect of the left frontal lobe and eroded its substance, rupturing into the left lateral ventricle. All the ventricles were filled with blood.

CASE 13.—A 63-year-old white woman was found unconscious in her home on the morning of admission, June 15, 1953.

On examination she was comatose, with Cheyne-Stokes breathing. Blood pressure was 200/126. There was a right lower facial paresis. The pupils were small and did not react to light. There was a right hemiparesis, with positive Babinski and Hoffman reflexes bilaterally. A lumbar puncture done the day after admission showed a pressure of 320 mm. of xanthochromic fluid. The patient developed pneumonitis and died nine days after admission.

Autopsy revealed a small aneurysm of the left anterior cerebral artery at a point about 1 cm. distal to the anterior communicating artery. On cut section of the brain there was softening and hemorrhage into the brain substance about the aneurysm. Both lateral ventricles and the third ventricle were filled with blood-tinged fluid which had entered via the left lateral ventricle.

CASE 14.—A 64-year-old white man was well until the morning of admission, Nov. 3, 1953, when he was awakened by severe occipital headache. He was nauseated and vomited several times.

On examination he was drowsy but was easily aroused. There was a questionably positive right Babinski sign. A lumbar puncture done three days after admission showed a pressure of 153 mm. of clear fluid. Sixteen hours after his last lumbar puncture his condition became worse, and he was noted to be responding poorly. He became gradually worse and died 17 days after admission.

At autopsy there was bilateral subdural hemorrhage. The left posterior communicating artery was a small vessel of almost capillary size. The anterior communicating artery was hypoplastic, and on the left no anterior cerebral artery was visualized. However, in the region where the anterior cerebral artery should originate there was a berry aneurysm 5 mm. in diameter which had ruptured into the brain substance and into the anterior horn of the left lateral ventricle and also through brain substance externally into the subarachnoid space. The ventricular system was distended with blood throughout. There were tentorial and cerebellar pressure cones bilaterally.

Comment.—Anatomy: Six of these fourteen cases originated from the anterior cerebral arteries, five on the left and one on the right. Five of the six showed left frontal or bilateral intracerebral hemorrhage with subsequent rupture into the left lateral ventricle, and thus all the ventricles. The sixth had also ruptured into the left

lateral ventricle and massively into the subarachnoid space. Blood filled all the ventricles in this instance also. In two of the six cerebellar pressure cones were noted.

Of the eight cases of aneurysm of the anterior communicating artery, five were of the anterior communicating artery alone and three were at the junction with one of the anterior cerebral arteries—one on the right and two on the left. Six of the eight had frontal hematomas which were usually large and half of which were bilateral. Four had a large amount of intraventricular blood; in three it was minimal, and in one case there was no intraventricular or intracerebral bleeding. In that case there was subarachnoid and subdural blood over the entire left hemisphere, and a moderate cerebellar pressure cone had been produced. In one other patient no intracerebral hemorrhage was found, but the ruptured aneurysm had poured blood into the third ventricle through the anterior perforated space and had distended the fourth ventricle to 10 times its normal size.

Thus there were, of the 14 cases, 13 which had ruptured into the ventricular system, some massively and some with just a small amount of hemorrhage. Twelve had formed one-sided or bilateral frontal hematomas, which were quite large in some cases. One had ruptured into the lateral ventricle without much cerebral damage, and one had penetrated directly into the third ventricle.

Symptoms and Signs in Relation to Cause of Death: In two cases the first episode was fatal, in eight there were two episodes of bleeding, and in four there were three or more. It is felt that enumeration of symptoms prior to the fatal episode are beyond the scope of the present study. In correlating the symptoms, signs, and clinical course of the fatal episode in relation to bleeding into regions other than the subarachnoid space the following features were noted.

Of the four cases with hemorrhage into both frontal lobes, two were characterized by rapid onset of coma and death with no localizing signs and two had generalized convulsions preceding the deep coma and death. There were no real localizing signs.

Of the eight cases of bleeding into one frontal lobe, three had the onset of coma, (in two of the three it was a sudden coma with a rapid course); there were generalized convulsions in two patients (with a localizing component in one). Half of the eight had a gradual downhill course, and in half death was fairly sudden. In two of the eight, death followed lumbar puncture in one and six hours. Whether or not there was a definite causal relationship cannot be told from the records.

In one case of subdural bleeding there was sudden worsening of the patient's condition with rapid death after a progressive two-week course.

In another case direct rupture into the third ventricle caused death within a few hours with no definite localizing signs. The remaining patient with rupture primarily into the ventricular system had a progressive downhill course over an eight-day period, with minimal lateralizing signs at first but none later.

There was usually a good relationship between the amount of intraventricular bleeding and the time until death with the final episode of bleeding. In 9 of the 14 this relationship was close, in 2 there was fair correlation, and in 3 there seemed to be no correlation, although the clinical course of some of the latter was complicated by operative procedures. That is, when there was massive bleeding into all the ventricles with dilatation of the ventricles the patient usually lived less than 6 hours; when all the ventricles were filled but not dilated with blood the patient died within 48 hours, and when there was very minimal or no intraventricular blood the patient usually lived 6 days or longer after his final episode.

In Robertson's[26] series of 36 ruptured aneurysms of the anterior cerebral or anterior communicating artery, 35 displayed intracerebral rupture, of which 17 were bilateral into both frontal lobes. There were 6 cases in which there was only superficial

erosion of one or both frontal lobes and 11 cases of hemorrhage into one frontal lobe. He noted one case of rupture into the third ventricle, and in one case there was subarachnoid bleeding only. He notes the frequent occurrence of coma and convulsions as a consequence of rupture into the frontal lobes. Walker,[24] in a recent review of symptoms associated with aneurysms notes that there is no typical picture clinically of aneurysms of the anterior cerebral or anterior communicating arteries. No attempt is made in his series to differentiate between symptoms before and after formation of intracerebral clot.

Internal Carotid Artery Group: Six Cases

CASE 15.—A 24-year-old white man was hit at the base of the skull by a blackjack 10 days before admission. After this he had a slight headache. The next day he noted the onset of a violent headache when he turned his head. He walked to a local hospital, where a lumbar puncture showed a pressure of 300 mm. of bloody fluid. The headache gradually cleared, and he entered here on Nov. 10, 1954.

On examination he was somewhat somnolent. There was blurring of the nasal portions of both optic discs. A lumbar puncture showed a pressure of 160 mm. of clear fluid. Four days after admission he suddenly grasped his head and called for a doctor. He became unresponsive and developed a right hemiparesis. The eyes deviated to the left; the right pupil was slightly larger than the left. Later he seemed to suffer another episode. He was paralyzed on both sides, and both pupils were dilated and unreactive. There were pathologic Hoffman and Babinski reflexes bilaterally. A left carotid arteriogram showed a 1 cm. aneurysm about 3 mm. below the bifurcation of the internal carotid artery. At operation there was resection of the premotor portion of the left frontal lobe and internal clipping of an aneurysm of the left internal carotid artery (preceded by ligation of the internal carotid artery in the neck). He did not improve and died two days after operation.

Autopsy showed surgical absence of the left prefrontal region and clips on both sides of a berry aneurysm of the left internal carotid (Fig. 3). Diffuse subarachnoid hemorrhage had erupted into the brain substance and lateral ventricle on the left, destroying the left putamen, globus pallidus, and head of the caudate nucleus. There were marked temporal and cerebellar pressure cones, with edema and compression of the brain stem.

CASE 16.—A 35-year-old white woman was found unconscious the morning of admission, on Jan. 3, 1953. A lumbar puncture done elsewhere showed grossly bloody fluid at a pressure of 200 mm. of water.

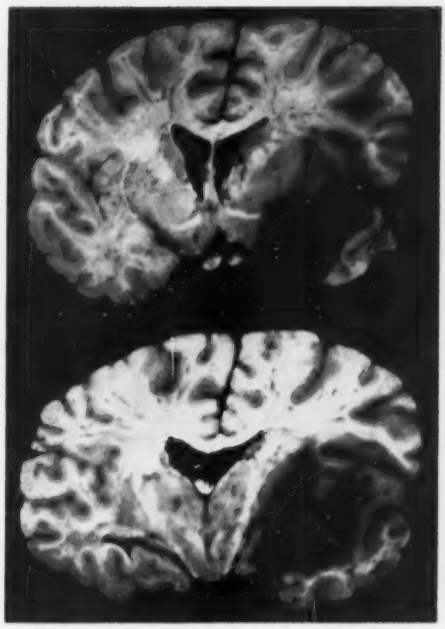


Fig. 3 (Case 15).—Ruptured "berry" aneurysm of the left internal carotid artery; subarachnoid, intracerebral, and intraventricular hemorrhage (into the left lateral ventricle).

On examination she was very restless and resistant. Her jaws were firmly closed, and she would not respond to questioning or command. The legs were flexed, and the neck was very stiff.

A lumbar puncture the day after admission showed a pressure of 140 mm. of grossly bloody fluid. The next day she had headache and vomited. Five days after admission arteriograms showed an aneurysm on the left internal carotid just proximal to the bifurcation. At operation the left internal carotid artery was occluded in the neck, and after a left frontal craniotomy, clips were placed on the internal carotid artery distal to the aneurysm. A small amount of intracerebral clot was removed from the undersurface of the frontal lobe. Shortly after the operation the patient exhibited signs of respiratory obstruction, and she died.

At autopsy a small aneurysm of the left internal carotid, just at its bifurcation and surrounded by clotted blood, was seen (Fig. 4). There was softening in the operative region, with moderate hemorrhage in the left frontal lobe where the intracerebral clot was removed. The cerebral ganglia on the left were softened also. The ven-

Fig. 4 (Case 16).—Aneurysm at the junction of the left internal carotid and posterior communicating arteries.

tricles were filled but not distended with blood. Bilateral cerebellar pressure cones were present.

Case 17.—A 49-year-old white woman had, since a fall on the ice four to five years before admission, been troubled with sick headaches. She stated that her head seemed about to burst while straining at stool or coughing, and there was some associated nausea and vomiting. Four days before admission, following a sudden "snapping" sensation in the frontal region, she complained of severe temporal-occipital headache. The morning of admission, July 12, 1954, she had a severe attack of pain associated with nausea and vomiting.

On examination there was questionable left visual field defect and a large hemorrhage above the right optic disc. The deep tendon reflexes were hyperactive on the right, and there was minimal nuchal rigidity. A lumbar puncture on the day of admission showed grossly bloody spinal fluid. On the fifth day after admission she had a transient episode of unresponsiveness. Later she became comatose. A right carotid arteriogram showed a 2×1 cm. aneurysm arising from the right internal carotid artery just below its bifurcation. The next day the right internal carotid artery was ligated in the neck and intracranially distal to the aneurysm. A subdural hematoma 0.5 cm. thick was noted over the right frontal region. The next day the left arm and leg moved less well than the right, and the patient died.

At autopsy a moderate amount of subdural and epidural hemorrhage was seen under the bone flap. A 1×0.5 cm. aneurysm of the right internal carotid artery just proximal to its bifurcation had ruptured into the subarachnoid space and into the inferior surface of the right temporal lobe (Fig. 5). It had penetrated into the temporal horn of the right lateral ventricle, filling all the ventricles with clotted blood. Marked temporal and cerebellar pressure cones were present.

Case 18.—A 42-year-old white man had complained of headaches for six to eight months before admission. Two weeks before admission he developed severe left-sided headaches. On the night of admission, Feb. 11, 1955, he was found on the floor unconscious.

On examination the patient was lucid and cooperative. There was no neurologic deficit. Soon afterward the patient had a grand mal convulsion with turning of the head and eyes to the right. He became comatose, and the breathing was Cheyne-Stokes in type. Nine hours after admission bilateral trephines were done. No subdural blood was found. The patient was in extremis and died on the operating table.

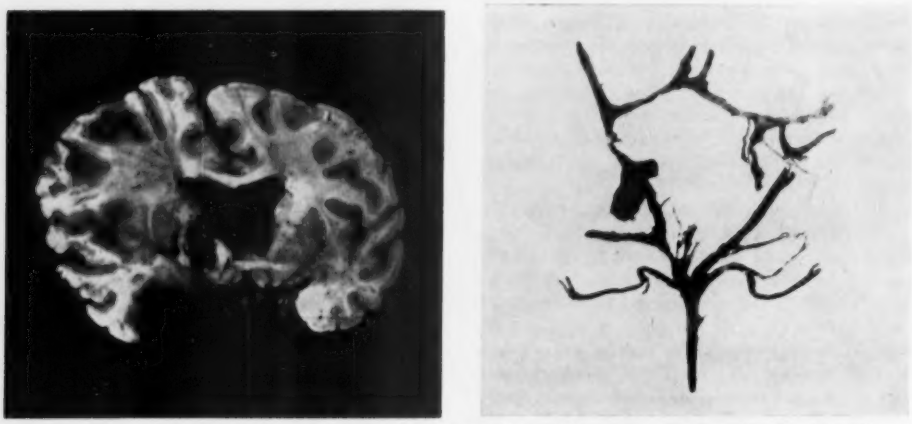


Fig. 5 (Case 17).—Aneurysm of the right internal carotid artery, causing subarachnoid and intracerebral hemorrhage into the right temporal lobe, basal ganglia, and lateral ventricle.

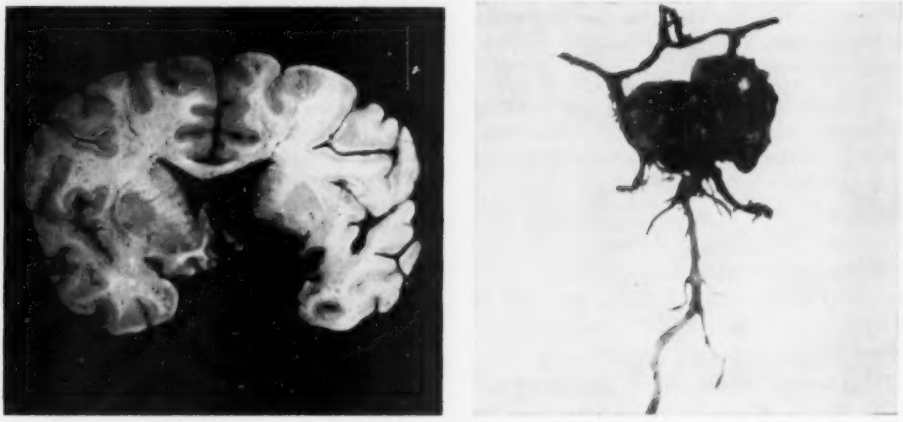


Fig. 6 (Case 18).—Large aneurysm of the left posterior communicating and left internal carotid arteries, with rupture into the subarachnoid space, left cerebral hemisphere, and thus intraventricularly.

At autopsy abundant subarachnoid blood was found. A large 3.5×3×1.5 cm. aneurysm at the juncture of the left internal carotid and posterior communicating arteries had ruptured, causing intracerebral hemorrhage, laceration of the basal ganglia, and intraventricular hemorrhage (Fig. 6).

CASE 19.—A 47-year-old white man was well until three weeks before admission, when he had the sudden onset of headache and unconsciousness. Two weeks before admission he had a second episode, and a third one occurred the day before admission. An arteriogram the day of admission at another hospital was said to show a mass in the right temporal lobe.

Admission examination on June 7, 1954, showed a comatose man whose respirations were Cheyne-Stokes in character. There was a complete flaccid left hemiplegia and a dilated pupil and external deviation of the right eye. On the day of admission operation revealed a small subdural hematoma, and a large intra-cortical clot in the right temporal lobe was evacuated. The right external and internal carotid arteries in the neck were ligated. The patient died six days after admission.

At autopsy there was minimal subdural hemorrhage. There was hemorrhage, softening, and necrosis of the right temporal lobe and orbital surface of the right frontal lobe, which extended into the right lateral ventricle. There was a pressure groove of the right uncus and a cerebellar pressure cone. Just below the bifurcation there was a 1×1.5 cm. aneurysm of the right internal carotid artery.

CASE 20.—A 48-year-old white woman complained of right upper quadrant pain and was admitted on May 31, 1940.

Examination showed no neurologic abnormalities. Six days after admission she complained of "migraine" headache and within three hours became comatose and died.

On examination of the brain there was an aneurysm 1 cm. in diameter at the junction of the right middle cerebral and internal carotid arteries which had ruptured. There was massive subarachnoid and subdural blood over the entire base of the brain, extending back and surrounding the cerebellum. There was no intracerebral or intraventricular hemorrhage.

Comment. — Anatomy: There were no cases of infraclinoid internal carotid artery aneurysm in this series. Two were just below the bifurcation on the right and two on the left. Two were at the junction of the left internal carotid and the posterior communicating arteries. Five of the six ruptured into the cerebrum on the affected side and then into the lateral ventricle, usually giving only moderate intraventricular hemorrhage. The remaining case ruptured into the subarachnoid and subdural spaces with no intracerebral or intraventricular hemorrhage.

Symptoms and Signs in Relation to Cause of Death: In five of the six cases operative procedures complicated the clinical course so that the actual consequences of rupture into the temporal lobe and basal ganglia unilaterally (for this was usually the case) are hard to determine. However, it is seen that there was one episode of bleeding in three, two episodes in two, and three epi-

sodes in one case. Three of the five cases that underwent operation died within 48 hours after operation, but it was felt that death in these cases was more or less inevitable (as judged by the autopsy findings). Therefore, they have been included in the present series in contrast to five cases not included because it was felt that operation was the primary cause of death.

With the last episode of bleeding there were definite lateralizing signs in four of the six cases. These signs varied in prominence from an obvious hemiplegia to minimal weakness on one side. The other two patients were comatose and demonstrated no localizing signs. Walker states that there is no typical clinical picture of ruptured aneurysm in this location.

The relationship between length of survival and intraventricular bleeding is also impossible to determine in the cases with operation. The one case with marked subarachnoid and subdural bleeding died within three hours.

Of Robertson's five cases of ruptured aneurysms at the termination of the internal carotid (he also reported none of the infraclinoid portion), two showed subarachnoid hemorrhage alone, one ruptured into the temporal lobe, one ruptured into the thalamus, and one eroded the temporal lobe superficially. Three aneurysms at the junction of the internal carotid and posterior communicating arteries all ruptured into the subarachnoid space alone.

Middle Cerebral Artery Group: Six Cases

Case 21.—A 39-year-old white man had had hypertension for the last eight years. One week before admission, while bending over, he noted the onset of severe aching headache associated with a "snapping" sensation in his head. One hour later he experienced nausea, vomiting, and dizziness.

Examination on admission on Oct. 25, 1948, showed an obese man in no distress. There was some nuchal rigidity. Examination of the optic fundi showed engorged veins bilaterally with no venous pulsations, but no papilledema. The left pupil was slightly larger than the right.

Spinal fluid examination three days after admission showed a pressure of 700 mm. of grossly bloody fluid. Three days after admission the patient was found lying on the floor, but he helped himself into bed. Following this he had several extensor spasms which became convulsions and later developed a left hemiparesis. By evening of the same day the patient was dead.

Autopsy showed a large mass of clotted blood surrounding the basilar vessels. There was a small pea-sized ruptured aneurysm of the middle cerebral artery on the right. There was a large 10×5×5 cm. blood-filled cavity running beneath the right cortex parallel to the ventricles which had ruptured into the right lateral ventricle. All the ventricles contained fluid and clotted blood.

Case 22.—A 49-year-old white man was well until three days before admission, when he complained of severe pain in the right frontal-parietal region. The next day he showed some improvement, but he was very restless.

Examination on admission, on May 4, 1942, showed a patient who was quite sleepy but not comatose. There was papilledema bilaterally and slight weakness of the right corner of the mouth. The neck was quite stiff. A lumbar puncture the day of admission showed xanthochromic fluid at a pressure of 400 mm. Several more punctures were done. Examination three days after admission showed a left lower facial paralysis and weakness of the left arm and leg. Five days after admission the patient apparently had another episode of bleeding, and he died the next day.

Autopsy showed subarachnoid hemorrhage over the base of the right temporal and parietal lobes, which were moderately enlarged and soft. A blood clot extruded through the lateral wall of the parietal lobe. There was an aneurysm in the midportion of the right middle cerebral artery. Hemorrhage had destroyed the white matter of the right temporal lobe, the insula, and the posterior right putamen. There was recent hemorrhage in all the ventricles.

Case 23.—A 33-year-old man was well until five weeks before admission, when he noted weakness of both lower extremities. He developed a severe headache and was taken to another hospital, where five lumbar punctures all showed bloody fluid. He returned home and was well until one day before admission, when he noticed sudden severe knife-like pain in the right jaw. This spread to the right temporal regions. His left hand jerked, and he noticed a loss of feeling in his left hand and arm.

On admission, on Aug. 3, 1947, he had a stiff neck. There was a left hemiparesis and hypesthesia. Lumbar puncture showed a spinal fluid pressure of 550 mm. of bloody fluid. Early the day after admission the patient was found dead in bed.

Autopsy showed subarachnoid blood over the entire right hemisphere. The right hemisphere was larger than the left. The right posterior communicating artery was underdeveloped. There was a

small aneurysm of the right middle cerebral artery which had ruptured in the sylvian fissure, producing massive hemorrhage involving the white matter of the frontal lobe and extending to the parietal and the occipital lobe. There was massive destruction by the hemorrhage of the lenticular nucleus and part of the internal capsule on the right. There was no blood in the ventricles.

CASE 24.—A 33-year-old Negro woman, one month before admission, developed a right-sided headache and entered another hospital. Headaches persisted during that hospitalization, but her hypertension improved. She was at home one week until her admission on Dec. 21, 1951.

On examination there was moderate neck stiffness, a right third nerve paralysis, and a left hemiparesis.

A lumbar puncture the day of admission showed a pressure of 190 mm. of cloudy fluid. The patient was more alert the morning after admission, but was found comatose and frothing at the mouth the same afternoon, and respirations soon ceased.

Autopsy showed subarachnoid hemorrhage about the pons. In the right temporal lobe there was a massive intracortical hemorrhage and necrosis, with extensive bleeding into the ventricles. The entire ventricular system was filled, and the fourth ventricle was widely dilated with clotted blood. A ruptured aneurysm, probably of the right middle cerebral artery, was seen.

CASE 25.—A 20-month-old white boy was well until the day of admission, on Oct. 4, 1952, when he vomited, convulsed and became unconscious. A lumbar puncture elsewhere showed grossly bloody spinal fluid.

On admission he was thrashing around his bed. There was subhyaloid hemorrhage and a left hemiparesis. A lumbar puncture showed bloody spinal fluid. Later the same day there was a generalized convulsion followed by a respiratory paralysis, and the patient soon died.

At autopsy there was, at a point 1.5 cm. beyond the point of origin of the middle cerebral artery, a large nodular aneurysm measuring 3×2 cm. This was surrounded by blood clot. The aneurysm was made up of multiple dilated pea-sized nodular masses filled with coagulated blood. Coming from this mass on the internal surface were multiple small blood vessels. Going from it were two blood vessels which were apparently a continuation of the middle cerebral artery. Proximal to this original aneurysm was a small aneurysmal dilation 2 mm. in diameter. In the region of the right middle cerebral artery there was a large blood clot involving the internal capsule, basal ganglia, thalamus, and hypothalamus. Hemorrhage entered the right ventricle and filled the entire ventricular system, causing moderate dilatation.

CASE 26.—A 48-year-old white woman had had right frontal and temporal headaches for one year before admission. About three and one-half weeks before admission she became unconscious and woke up in another hospital six days later with a "teriffic" headache. She improved but vomited several times and became unconscious the day of admission.

Examination on admission, on July 10, 1953, showed an old hemorrhage in the fundus of the right eye. The neck was stiff, and there were positive Babinski reflexes bilaterally. Lumbar puncture revealed a pressure of 340 mm. of bloody fluid. The night of admission the patient became worse. Later a left hemiparesis was noted. Her course was poor, and she died 15 days after admission.

At autopsy there was a ruptured aneurysm of the right middle cerebral artery where it branched into the circle of Willis. There was much recent subarachnoid hemorrhage, and the aneurysm had ruptured into the right temporal lobe and had communicated with the right lateral ventricle. All the ventricles contained blood.

Comment.—Anatomy: By coincidence all of the six cases of middle cerebral artery aneurysm were on the right side. They usually ruptured primarily into the temporal lobe, with some spread into the surrounding areas. Five of the six ruptured into the lateral ventricle on that side. The sixth demonstrated massive intracerebral hemorrhage in the white matter from the frontal to the occipital pole but no intraventricular bleeding.

Symptoms and Signs in Relation to Cause of Death: In one case (a 20-month-old child) there was only one episode of bleeding, in four cases there were two, and in one case it was the third episode that was fatal. All six of these patients demonstrated a left hemiparesis or hemiphegia with the final episode. This was more marked in some than in others. Walker noted one-sided weakness in 15 of his 28 cases of middle cerebral artery aneurysm, but added that there was no typical clinical picture of aneurysm in this location. Seven of Frankel and Alpers'[23] eight autopsied cases of middle cerebral artery aneurysm demonstrated intracerebral bleeding, and six of the seven had developed one-sided signs before death. They too felt that there was no typical picture and that the development of hemiplegia was a late manifestation and followed rupture of the aneurysm.

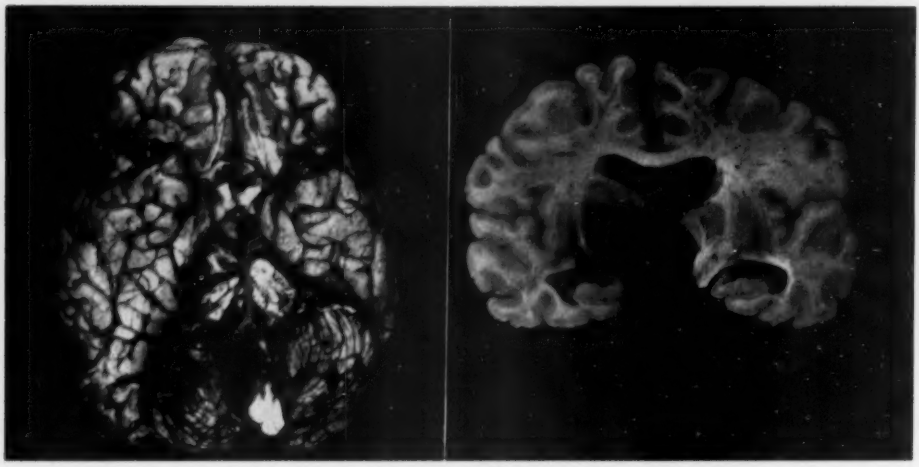


Fig. 7 A (Case 27).—Aneurysm of the right posterior cerebral artery, with rupture into the subarachnoid space, right cerebral hemisphere, and third ventricle.

Robertson's personally investigated series included four autopsied cases of ruptured aneurysm of the middle cerebral artery, two of which had ruptured into the temporal lobe and two into the frontal lobe. He also recorded 32 cases from his records, 8 of which demonstrated subarachnoid hemorrhage alone; the other 24 had ruptured into the temporal, frontal, parietal, or occipital lobe.

There was a close relationship in four cases of the present series between time from the last hemorrhage until death and amount of bleeding into the ventricles. In one case there was no relationship. This was a case in which there was no intraventricular bleeding, but massive intracerebral clot with rapid death. In the remaining case there was a fair relationship. None of the six underwent operation, but all six had had lumbar punctures. In five of the six death occurred within two days after lumbar puncture, but a causal relationship was impossible to determine with any certainty.

Fig. 7 B (Case 27).—Showing the third cranial nerve over the surface of the aneurysm.

Posterior Cerebral and Posterior Communicating Artery Group: Four Cases

CASE 27.—A 59-year-old woman was well until May 22, 1954, when she suddenly complained of severe headache, became semicomatose, and entered the hospital soon afterward.

On examination she was semicomatose and demonstrated a complete right third cranial nerve palsy and a left flaccid hemiplegia. Lumbar puncture showed a pressure of 440 mm. of grossly bloody fluid.

The day of admission the patient had a generalized convulsion followed by complete coma. She became worse and died the next day.

Autopsy showed a large aneurysm of the right posterior cerebral artery which had compressed the right third nerve and caused an erosion of the right cerebral peduncle (Fig. 7). It had ruptured through the posterior perforated space and had destroyed the walls of the third ventricle, the tegmentum of the midbrain on the right, and the right thalamus. All the ventricles were filled with blood. Marked bilateral cerebellar pressure cones were present.

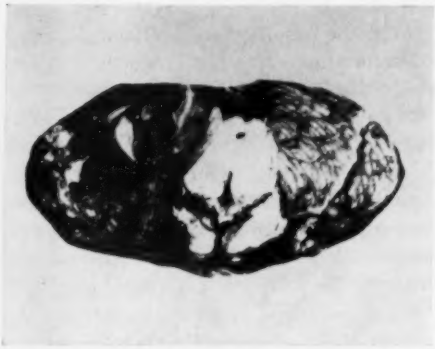


Fig. 8 A (Case 28).—Showing compression of the cerebellum and midbrain by an aneurysm of the right posterior cerebral artery.

Fig. 8 B (Case 28).—Cross section of the aneurysm of the right posterior cerebral artery.

CASE 28.—An 18-year-old white girl 16 months before admission struck her head on a bed. She had intermittent headaches since. The day preceding admission the patient had one steady headache, lapsed into coma, and began convulsing.

Examination on admission, June 9, 1951, showed tonic and clonic movements and thrashing about of the right upper and lower extremities. The pupils were pinpoint at first and then dilated and did not react to light. There was bilateral papilledema. A ventricular tap on the right revealed old blood clots and macerated brain substance. Lumbar puncture showed a pressure of 350 mm. of bloody fluid. She died the day after admission.

At autopsy there was abundant fresh blood over the base of the brain. There was an aneurysm 3 cm. in diameter of the right posterior cerebral artery (Fig. 8). It had ruptured and destroyed the right cerebral peduncle and the surrounding gyri and had gone into the ventricular system through the right temporal horn, filling the lateral, third, and fourth ventricles and the aqueduct.

CASE 29.—A 54-year-old white woman had three episodes of headache, nausea, vomiting, and loss of consciousness beginning three months before admission. She also had decreased vision in the right eye and right-sided weakness.

Examination on admission, on March 3, 1940, showed blurring of the nasal margin of the right disc and a third and fourth cranial nerve paralysis on the right with minimal weakness of the right leg.

Lumbar puncture two days after admission showed a pressure of 250 mm. of xanthochromic fluid. Three days after admission she was found dead in bed.

Autopsy showed massive subarachnoid hemorrhage over the base of the brain. There was a ruptured aneurysm of the right posterior cerebral artery. The hemorrhage had broken into the ventricular system on the right side via the right temporal lobe and thus into all the ventricles. There was hemorrhage and necrosis of the right temporal lobe.

CASE 30.—A 34-year-old white man complained of an excruciating headache the day of admission and soon became unconscious.

Examination on Feb. 4, 1947, showed a comatose man with small pupils, slow respirations, and pathological Babinski reflexes bilaterally. Respirations ceased 15 hours after admission (no lumbar puncture was done).

Autopsy showed a ruptured aneurysm 2×1 cm. at the junction of the right posterior cerebral artery with the posterior communicating artery. Hemorrhage extended into the brain substance on the right, penetrating into the temporal lobe and thus into the lateral ventricle. It had destroyed a large portion of the temporal and parietal lobes, the caudate nucleus, globus pallidus, and the putamen on the right. All the ventricles were filled with blood.

Comment.—Anatomy: Three of the four aneurysms were located on the right posterior cerebral artery, and the remaining one was at the junction of the right posterior cerebral and posterior communicating arteries. Three had ruptured into the cerebral substance on the right (into the temporal lobe) and then had penetrated to the right lateral ventricle, thus pouring

blood into all the ventricles. The fourth had ruptured through the posterior perforated space into the third ventricle and had caused all the ventricles to be distended with blood, thus producing a cerebellar pressure cone.

The first episode of bleeding was fatal in three cases; in the fourth there were two.

Symptoms and Signs in Relation to Fatal Hemorrhage: In spite of the fact that three of the four demonstrated unilateral intracerebral rupture, there was only one recorded hemiplegia. Two patients had generalized convulsions with their fatal hemorrhage, and in two there were third cranial nerve palsies preceding the fatal episode. This latter fact is explained by the location and size of the aneurysm; three of the four were quite large (up to 3 cm. in diameter).

In three of the four cases there was a close relationship between the amount of intraventricular bleeding and the time from the last rupture until death. In the remaining case there was a fair relationship between the two.

Death in two followed within 24 hours of a lumbar puncture, but again the connection between them is not obvious. In the one case subjected to operation it is thought that it neither speeded nor delayed death.

Walker, in reviewing his cases of aneurysm of the posterior cerebral and posterior communicating arteries, found 10 cases which displayed symptoms similar to the present series. He concluded that his series was too small to draw any conclusions as to diagnostic clues. Ours certainly is too. Robertson found five aneurysms in this location, of which two ruptured into the temporal lobe, one into the thalamus, and two into the subarachnoid space only.

Basilar and Vertebral Artery Group: Five Cases

Case 31.—A 39-year-old white man had the onset of severe headache, loss of vision, left hemiparesis, and inability to talk five days before admission. He became semicomatose, and a lumbar puncture elsewhere showed bloody spinal fluid. He improved and was admitted on April 9, 1954.

On examination he was lethargic, irritable, and restless. There was bilateral subhyaloid hemorrhage, ptosis, weakness of upward and lateral gaze, and loss of conjugate eye movements. There were bilateral pathologic Babinski responses and mild ataxia in the right upper extremity. The patient's condition gradually deteriorated, and he died nine days after admission.

At autopsy an aneurysm 0.5×0.5 cm. was found at the bifurcation of the basilar artery (Fig. 9). A large blood clot surrounded it and extended from the medulla to the optic chiasm. Blood was found in the posterior third ventricle, the aqueduct, and the dilated fourth ventricle. There was diffuse hemorrhage in the pons, cerebellum, and medulla. There were bilateral cerebellar pressure cones.

Case 32.—A 41-year-old woman three hours before admission was found in her room groaning,

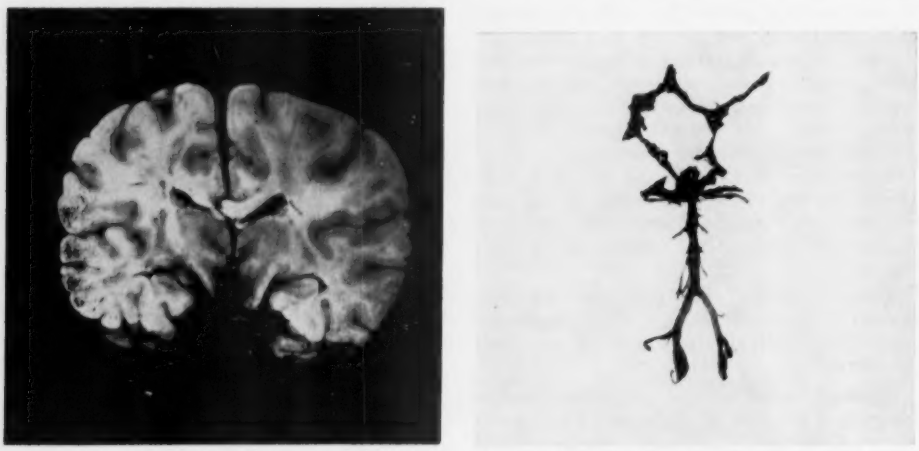


Fig. 9 (Case 31).—Small ruptured aneurysm at the bifurcation of the basilar artery with rupture into the third ventricle (intraventricular and subarachnoid hemorrhage).

unconscious, and frothing at the mouth. Convulsive seizures followed, and she was admitted on Jan. 25, 1937.

Examination showed rapidly developing pulmonary edema. Ten minutes following admission to the ward the patient's respirations ceased.

Autopsy showed blood clot over the base of the brain. At the bifurcation of the basilar artery arose an aneurysm 1 cm. in diameter which had ruptured near its base. All the ventricles contained clotted blood but were not particularly distended. The tissue surrounding the third ventricle was soft, as were the pons, medulla, and peduncles. Blood extended down the spinal canal.

CASE 33.—A 61-year-old white woman had the first of three "strokes" with left hemiparesis 14 years before admission. She also had diabetes and auricular fibrillation. She had an occipital pain and loss of consciousness the night before admission.

Examination on admission, March 22, 1954, showed a blood pressure of 220/110 in a comatose patient. There was auricular fibrillation. The left pupil was larger than the right, and the fundi showed marked hypertensive changes with hemorrhages and exudates with blurring of the disc margins. Deep tendon reflexes were absent on the left side, and the neck was stiff. Three days after the onset the patient died (a lumbar puncture was not done).

At autopsy a ruptured aneurysm 8 mm. in diameter was found at the rostral end of the basilar artery. There was subarachnoid hemorrhage over the base of the brain which had entered the ventricular system through a laceration in the floor of the third ventricle. The ventricular system was dilated and filled with serosanguinous fluid.

CASE 34.—A 36-year-old white man one week before his first admission had a sudden severe pain in the back of his neck. Lumbar punctures at another hospital were done for relief of pain; all revealed bloody spinal fluid. On his first admission, from Dec. 15 to Dec. 30, 1951, he was disoriented and moaning with pain. Blood pressure was 200/110, and there was marked nuchal rigidity. The patient was treated with hypotensive drugs and gradually improved. He left the hospital and did all right for two days at home but on the third day suddenly became unconscious and when he awoke was incoherent. He was readmitted on Jan. 4, 1952. Examination showed a blood pressure of 160/88. There were moderate meningeal signs. The day after admission a lumbar puncture showed a pressure of 380 mm. of xanthochromic fluid. One and one-half hours after this the patient suddenly became unconscious and died within a few minutes.

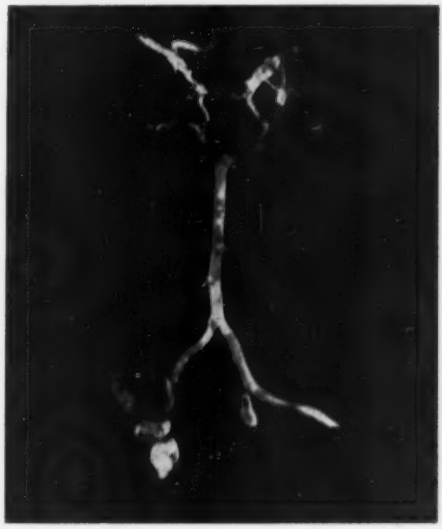
At autopsy an aneurysm 4 mm. in diameter was seen at the bifurcation of the basilar artery. This had ruptured into the third ventricle, causing all the ventricles to be dilated and filled with clotted blood which had escaped through the roof of the fourth ventricle to surround the medulla and pons. There was no intracerebral hemorrhage. A photograph of this aneurysm can be found elsewhere.[37]

CASE 35.—A 35-year-old Negro woman was first admitted on July 2, 1950. She had had a sudden severe headache over the right eye the night before admission. Examination showed nystagmus in all directions of gaze and ptosis of the right eyelid. The left pupil was larger than the right. There was a right peripheral facial weakness and some slurring of the speech. The tongue deviated to the right. There was hypesthesia on the left half of the body. There was bilateral ataxia. She was discharged on July 29, 1950, much improved, and did well until four days before her last admission, on March 27, 1952, when she complained of headache and had a convulsion.

On examination she was unconscious and held her arms rigid and flexed, with her legs stiff. The eyes were deviated upward and to the left, and the pupils were large and did not react to light. There were large fresh hemorrhages seen in the left fundus. She had a stiff neck. A lumbar puncture on the day of admission showed a pressure of 125 mm. of grossly bloody fluid. A repeat puncture showed no change three days after admission. Respirations ceased the next day.

At autopsy there was an aneurysmal dilatation near the junction of the right vertebral and anterior spinal artery (Fig. 10) which measured 2×1 cm. and was perforated on its lateral

Fig. 10 (Case 35).—Ruptured aneurysm of the right vertebral artery (rupture into the subarachnoid space and cerebellum). Small unruptured aneurysm of the left vertebral artery.



superior aspect. An unruptured 5 mm. aneurysm of the left vertebral artery with a 5 mm. stalk was also present. There were areas of subarachnoid hemorrhage beneath the posterior part of cerebral hemispheres and about the cerebellar hemispheres. The entire ventricular system was filled with fluid blood. There was clotted blood within the right cerebellar hemisphere which connected with the blood in the fourth ventricle and thus with the hemorrhage surrounding the cerebellum. There was a moderate cerebellar pressure cone.

Comment. — Anatomy: The four aneurysms of the basilar artery were all at the bifurcation and all ruptured or eroded into the third ventricle through its floor, causing either local damage with minor bleeding or massive intraventricular hemorrhage. The aneurysm of the right vertebral artery had ruptured into the fourth ventricle and thus into the right cerebellar hemisphere.

There were three episodes of bleeding in one patient, two in two, and one episode in two patients.

Symptoms and Signs in Relation to Fatal Hemorrhage: In all but one case the fatal episode was simply one of sudden unconsciousness followed fairly rapidly by death with no localizing signs, although there may have been signs before the final hemorrhage that would have enabled one to locate the lesion in the posterior fossa.

Two lumbar punctures were done in these five cases; death followed in 1½ hours in one and in 24 hours in the other. Again, we cannot be certain of the causal relationship in these cases. No operations were done.

There was a close relationship between the amount of intraventricular bleeding and the time from the fatal hemorrhage until death in one case and a fair relationship in the remaining four cases. Two of Robertson's series were of the basilar artery. Both showed subarachnoid hemorrhage alone with no intracerebral or intraventricular hemorrhage.

General Comment

When the above findings were summarized it was found that, of the 35 cases, 26 demonstrated both intracerebral and intraventricular hemorrhage, 6 ruptured primarily intraventricularly, 2 ruptured primarily subdurally, and 1, intracerebrally. All of these showed subarachnoid bleeding also.

Eleven patients died of the first episode of bleeding; seventeen, with the second, and seven, with the third (or more).

The median age of these patients was 41 years. There were 20 males and 15 females in the series. There were no mycotic or syphilitic aneurysms.

Symptoms subsequent to the final fatal rupture were not always such as to enable a localizing diagnosis to be made. However, previous episodes sometimes gave a clue as to the location of the aneurysm, and if coma, with or without quadriplegia or hemiplegia, supervened it could usually be assumed that intracerebral, intraventricular, or subdural extension of the subarachnoid hemorrhage had taken place. With a hemiplegia the most likely source was found to be the anterior cerebral, middle cerebral, or internal carotid arteries; with bilateral pyramidal tract signs, it was found to be the anterior cerebral or anterior communicating arteries.

There was a good correlation between the amount of intraventricular bleeding and rapidity of death in 17 of the 29 patients in whom the comparison could be made. That is, in some of these cases blood had distended and filled all the ventricles and the patient died within six hours of the onset of his last episode; in others all the ventricles were filled but not distended and death occurred in 6 to 48 hours. In others there was blood in some of the ventricles and the patient lived two to six days. If there was no intraventricular blood (or very little) the patient lived longer than six days after the onset of his fatal episode. In eight cases the correlation was only fair, and in four there seemed to be no relationship. More will be said later about this relationship.

In considering this series several questions arise. Why is there a high incidence

of death with aneurysms of the anterior communicating or anterior cerebral arteries? Of McDonald and Korb's 786 ruptured aneurysms, only 17% were on the anterior communicating system, whereas 48% were of the internal carotid or middle cerebral. In both the present series and in Robertson's series of fatal cases closer to 40% were anterior communicating or anterior cerebral in nature. A suggested answer is that this is a more dangerous location for an aneurysm; that rupture here is more likely to cause intracerebral or intraventricular hemorrhage and death than rupture elsewhere on the circle of Willis or its branches.

Similarly, the incidence of fatal aneurysms of the termination of the internal carotid artery or the middle cerebral artery is less in the present series and in Robertson's series than in collections of nonfatal cases. No doubt these figures have a low statistical significance, but they do suggest that an aneurysm in these locations is less likely to be fatal than in others. In addition, neither series reports any fatal cases of infraclinoid internal carotid artery aneurysms with autopsy. This type also must have a low mortality rate.

It is noteworthy that none of the cases in the present series died of subarachnoid hemorrhage alone. Four cases of subarachnoid bleeding and cerebral infarction were eliminated before the series was analyzed, and it could be argued that these deaths were due to aneurysm just as much as those which bled profusely into the brain. This is no doubt true. However, it was felt that death was not due primarily to rupture, but to the associated cerebral infarction, whether it was due to spasm or thrombosis. These were, therefore, eliminated from the present series; we were left with 35 cases of death due to ruptured intracranial aneurysms, in which death in no case could be blamed on subarachnoid hemorrhage alone.

When the consequences of rupture in a gathering of cases from the literature are analyzed it is seen that in close to one-third death was held to be due to subarachnoid

Results of Hemorrhage from Aneurysms, as Obtained from Autopsy Reports

Authors	Cases	Subarachnoid Hemorrhage Alone	Subarachnoid Hemorrhage Plus					Subarachnoid Hemorrhage Secondary To	
			Intracerebral Hemorrhage	Intraventricular Hemorrhage	Subdural Hemorrhage	Intracerebral & Intraventricular Hemorrhage	Ischemic Infarct	Intraventricular Hemorrhage	Intracerebral Hemorrhage
Symonds[1,2]	3	1	1		1				
Wolfe[21]	47	25	5			7		9	1
Globus and Globus[22]	21	11		2		8			
Mitchell and Angrist[23]	36	20	5	5		5		1	
Hammes[24]	53	25	6	2		20			
Richardson and Hyland[25]	27	8	19						
Dial and Maurer[26]	9	2	1	3		3			
Frankel and Alpers[27]	8		6			1	1		
Robertson (own cases)[28]	12		3			6	3		
Robertson (from records)[28]	85	20	64	1					
Walton[29]	124	39	85						
Williams, Bahn, and Sayre[37]	88	31	14			43			
	35								
Present series	(39)		1	6	2	26	(4)		
Totals	552	182	210	19	3	119	8	10	1

hemorrhage alone (Table). This is only a representative sampling of the literature and is not intended to include all the known autopsied cases. In about 40% the main finding was intracerebral hemorrhage (plus subarachnoid hemorrhage). The remaining quarter was divided between the other pathways of hemorrhage. The intracerebral third is probably artificially high because some authors distinguished only between subarachnoid and intracerebral bleeding, so the latter probably includes many cases that should be classified otherwise (such as intracerebral plus intraventricular). Robertson's series is interesting in that the cases he personally saw showed no deaths from subarachnoid hemorrhage alone, in contrast to those from his records, which showed 20 of 85 deaths in this fashion. Likewise, none of Frankel and Alpers' personally investigated eight cases died of subarachnoid bleeding alone.

Are the 35 patients in the present series a true representation of deaths due to ruptured aneurysm? It seems likely that, when the deaths in any series of autopsied aneurysms due to pneumonia, operation, or ischemic infarction are eliminated, the remaining cases will demonstrate hemorrhage in additional spaces to the subarachnoid. It probably takes more than simple subarachnoid bleeding to cause death. There most likely must also be rupture subdurally, intraventricularly, or intracerebrally.

As was noted above, there is usually a good correlation between amount of intraventricular bleeding and rapidity of death. The chief exceptions to this are the cases of subdural, intracerebral (alone), and third-ventricle bleeding. In the three instances of subdural or intracerebral bleeding there was no intraventricular blood, and yet death came quickly. In all three the amount of bleeding was great enough to cause death in a manner similar to that of any large space-occupying lesion. The cases of third ventricular hemorrhage are a different matter; there was not a good correlation between amount of hemorrhage and time until death. It is possible that local destruction of areas surrounding the third ventricle played a part in the rapid death of these patients.

In 11 of these cases there was a possible relationship between worsening of the patient's condition and lumbar puncture. In a few the patient definitely became worse within an hour or two after lumbar puncture. Whether this is coincidence or not cannot be said, but various writers have been warning against carrying out excessive lumbar punctures since Oppenheim's day [2,25,28,29]; Robertson recently reiterated this thought, as did Walton.[36]

Summary and Conclusions

Thirty-five cases of autopsies after death due to ruptured intracranial aneurysms were examined.

It was found that none of these died of subarachnoid hemorrhage per se. There was also intracerebral hemorrhage in 1, subdural bleeding in 2, intraventricular hemorrhage in 6, and intracerebral and intraventricular bleeding in 26.

There was a close relationship between the amount of bleeding into areas other than the subarachnoid and the length of survival after the onset of the last, or fatal, hemorrhage.

In some of our cases there was thought to be a relationship between worsening of the patient's condition and lumbar puncture, but this could not be proven.

A short discussion of the signs and symptoms with the hemorrhage is given.

Deaths from intracranial arterial aneurysms are thought to be due to one or more of the following causes: hemorrhage, operation, ischemic infarction, pneumonia, or compression and obstruction by an unruptured aneurysm acting as a tumor mass.[30]

Deaths due to hemorrhage from ruptured intracranial aneurysms are thought to result from hemorrhage into areas other than (but usually in addition to) the subarachnoid space. The most common is intracerebral with or without intraventricular hemorrhage. Bleeding may also be primarily intraventricular or subdural.

Subarachnoid hemorrhage alone is not felt to be an adequate explanation for death from a ruptured intracranial arterial aneurysm.

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Syphilis

Review of the Recent Literature

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The chief theme of the activities in the field of syphilology during the period covered by this 21st annual review of syphilis (July 1, 1955, to July 1, 1956) is retrospection—a looking back to syphilis of the past. This is attested to by the relatively large number of publications on the history of syphilis. These include a book chiefly for the layman on the story of that still "Secret Enemy" [1] and an entire issue of the *A. M. A. Archives of Dermatology* devoted to certain aspects of the disease whose name has only recently been dropped from its masthead. This does not mean that new developments have been neglected. In fact, the outstanding study by Magnuson and his group on the inoculation with Treponema pallidum of human volunteers and the Oslo study of untreated syphilis are great contributions to syphilology, whether the conclusions are valid or not. In serology, the trial use of antigens made from virulent T. pallidum, more about Treponemal agglutination tests, and the newer data on the treponemal immobilization test are offered in addition to the conventional subjects, such as antigens and biologic false-positive reactions. Treatment has become reasonably stabilized, in the Western world at least, with penicillin the mainstay. Chief emphasis has been placed on the visceral aspects of syphilis, especially the cardiovascular phase. Penicillin reactions still cause considerable concern. In spite of diminished financial support, there is much effort, especially on the global level, in the area of control of the venereal diseases (syphilis).

The Third Annual Joint Statement on the Status of Venereal Disease Control in the United States continues to urge increased federal support of state and local veneral disease control programs, increased attention on the part of the federal government to venereal disease problems of migrant labor, collection of information and development of a program to prevent venereal disease among teen-agers, and congressional appropriation of $5,000,000 for federal assistance to states.

There are conflicting data with respect to the incidence of venereal disease (syphilis) and the need for control. One group reports a falling trend, while the other maintains that syphilis is still here. According to a report from Georgia,[2] venereal diseases are on the rise again. In the last six months of 1954, forty-three states reported a rise in cases of early syphilis or gonorrhea. The highest rates were in the age group of 20 to 24 years, many of whom acquired their infection during the teen years. A single infection in a middle Georgia city spread to 211 young people within six weeks, 70 of whom contracted syphilis. Many cases

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of venereal disease are now being found after the first symptoms have disappeared. In this way carriers of infection are active, usually within the group of young people. Young people whose infections go undiscovered and untreated are candidates for disability and premature death from one of the few easily preventable chronic diseases.

Vought et al.[3] consider the control of syphilis in New York State to be far from an accomplished fact. In order to induce a continued downward trend, these two aspects of control are emphasized: systematic efforts to locate the population groups most at risk of acquiring the disease by intensive epidemiologic studies and intensified control procedures in the groups thus located. A report of the North Carolina Venereal Disease Control Section[4] indicates a small decline in 1954, although the total treatment activity was increased because known contacts of gonorrhea and syphilis were treated on a prophylactic basis. There were two major venereal disease epidemics involving 75 persons in Chadbourn and 127 in Greensboro. More than one-half of those involved were teen-agers. Private physicians improved their reporting of syphilis cases. In 1954 they reported 26% of all cases in North Carolina, as compared with about 37% nationally. During the year, the three prevention and control centers in the state performed 27,830 diagnostic observations, in which 5048 venereal disease infections were identified. The same downward trend has been noted in England. King[5] presented data on patients at treatment centers in England and Wales. The number of patients with early syphilis was 6812 in 1949 and 1074 in 1953, showing evidence of a steady decline. The figures for gonorrhea showed no such decline. The rising incidence of nongonococcic urethritis was discussed.

Schamberg[6] reports that the rate of new syphilitic infections in the United States decreased by 93% between 1947 and 1954. Factors which have brought about this reduction, however, do not assure continued decline; periodic epidemics will remain a possibility until a method of immunization is developed. Generally, syphilis is most prevalent in wartime. Increased stability and prosperity of the population since the war is partially responsible for the observed reduction in incidence. Widespread use of penicillin in recent years has probably also contributed to the decline. Syphilis may be cured by the amount of penicillin commonly given for other diseases; use of repository penicillin preparations, which maintains high blood levels of the antibiotic for days or weeks, increases the probability of coincidental cure. Since the incubation period of syphilis is long, such medication may, in many instances, eradicate treponemes before any symptoms appear. A third factor in the decreased attack rate is the public health campaign against the disease. Education, contact investigation, mass blood testing, and provision of free treatment have resulted in discovery and cure of many infected persons. Public health measures must be continued and increased in order to keep incidence low. The number of susceptible persons rises when the attack rate is low over a prolonged period of time, and physicians are less likely to suspect syphilis. Under such conditions, future epidemics of syphilis may be started by seemingly minor factors. Reduction in the use of penicillin may lead to an increase in attack rate; broad-spectrum antibiotics replacing penicillin are less effective against syphilis.

Belief in the downward trend of syphilis is reflected by two recent actions. In the "New Edition of Hospital Accreditation Standards,[7] approved by The Board of Commissioners of the Joint Commission on Accreditation of Hospitals on Jan. 28, 1956, routine serologic test for syphilis is dropped:

> 1. The requirement that all patients on admission have a serologic test for syphilis has been dropped. This is now optional with the hospital. Hospitals should determine the legal requirements in their respective states concerning the serologic test for syphilis, especially those regarding obstetrical patients.

Also, *The Journal of the American Medical Association*, July 16, 1955,[8] reported the passage of a resolution to change the name

of The Section on Dermatology and Syphilology to The Section on Dermatology.

On the other hand, Porter[9] claims that in the state of Delaware there has been an increase in the reports of new infections of spyhilis since 1952. It is stated that there must still be a sizeable reservoir of cases which have not been detected or adequately treated. He feels that the battle against syphilis is not yet won. Likewise, Dennie[10] thinks that both the medical profession and the laity must be reacquainted with the fact that syphilitic disease is still a formidable factor in the list of contagious diseases in our country. Millions of people are still suffering from this disease. New cases run into the hundreds of thousands each year. In order to control syphilis and gradually eliminate it as an important factor in the health problem of the United States, a system of education must not only be carried on continuously, but more intensely. Similarly, Touraine[11] is opposed to any relaxation in the campaign against venereal disease. He believes that penicillin is not the only factor involved in the decline of venereal disease (syphilis). There are well-known cyclical fluctuations in the prevalence of these diseases. Therefore, early serological and clinical detection of unrecognized and latent cases and social measures against infections from home and abroad remain important. Crandell and his associates[12] conclude, from a survey of private patients and one in a psychiatric hospital, that in view of the number of patients with syphilis of the nervous and cardiovascular systems in a single institution, "Syphilis is Still Here." Fiumara, Appel, Hill, and Mescon,[13] who have reviewed the present status of syphilis and its management, reiterate that the venereal diseases are on the rise again and that syphilis is still a nation-wide problem. This means that a reservoir of infectious syphilis exists in most communities. There is also a residuum of noninfectious syphilis. All of these data indicate that syphilis will be a serious medical problem for many years.

The venereal diseases (syphilis) have been accorded considerable publicity during this review period. The entire May, 1956, issue of the *A. M. A. Archives of Dermatology*[6,26-39,41,42] was devoted as a commemoration to the occasion of the 50th anniversary of the Wassermann test. The lay press has given much space to syphilis and the other venereal diseases. For example, *Newsweek*, Dec. 5, 1955, gave two full columns in its section on medicine to "The Tainted Youth," an account of venereal diseases among teen-agers. *Time*, Feb. 13, 1956, described "The Venereal Disease Comeback." The *Chicago Sunday Tribune Magazine*, June 10, 1956, contained a long article by John A. Menaugh, entitled "The Fight Against Syphilis." *The Chicago Tribune* makes claim that in October, 1935, it was the first to react against the taboo of public publications mentioning syphilis. *The Philadelphia Evening Bulletin*, May 4, 1956, in Earl and Anne Selby's column, discussed the question of whether blood tests (for syphilis are necessary. Cleugh,[1] a layman, has presented the story of syphilis from its earliest beginnings. This book is designed in such a way as to give the average man a clear idea of what this disease has meant to the world in the past, thereby putting into his hands the one sure weapon with which to conquer this still "secret" enemy. The 25th Venereal Disease Postgraduate Course for physicians, sponsored by the University of Washington School of Medicine and the Public Health Service, was given in Seattle, March 19-23, 1956. The course was designed to acquaint the practitioner with the latest developments in diagnosis, treatment, and management of the venereal diseases.

The 1st International Symposium on Venereal Diseases and the Treponematoses, sponsored by the Public Health Service, U. S. Department of Health, Education, and Welfare, and the World Health Organization, was held at the Statler Hotel, Washington, D. C., from May 28 through June 1, 1956. This symposium afforded an ex-

cellent opportunity for authorities in the field from all over the world to exchange ideas and information on the latest developments in research, diagnosis, treatment, and case finding of the venereal and treponemal diseases. Invitations were sent to persons in many foreign countries with the cooperation of the World Health Organization, the International Union Against Venereal Disease and the Pan American Sanitary Bureau. Hundreds of physicians, scientists, and health workers, from all of the States and Territories of the United States, attended as a result of invitations extended through the Association of State and Territorial Health Officers, the American Academy of Dermatology and Syphilology, the American Venereal Disease Association, and the American Social Hygiene Association. The agenda for the symposium, as listed in current literature on venereal disease, covered such topics as "Control of Venereal Diseases and the Treponematoses in Retrospect and Prospect"; "Reporting and Statistical Problems"; "Natural History of Syphilis and the Treponematoses"; "Experimental Syphilis and the Treponematoses"; "Serology and Immunology of the Treponematoses"; "Diagnosis, Management and Prognosis of the Treponematoses and the Venereal Diseases"; "Gonorrhea, the Minor Venereal Diseases and Nongonococcic Urethritis"; "Epidemiology and Control Techniques"; "Health Education and Public Information"; "Voluntary Agency Cooperation in Control Programs." This symposium received considerable publicity in both the lay and the medical presses. *Medical News*, June 18, 1956, headlined, "Ask M.D. Help in Checking Rise of V. D." *Newsweek*, on June 11, 1956, discussed, "The Russians and V. D." This write-up was occasioned by the report at the symposium by Russian syphilologists that they were still treating syphilis with injections of bismuth and other metallic compounds, in long courses, including six weeks of hospitalization, which Western world physicians have discarded with the development of the antibiotics. According to this article, Professor Smelov contended that penicillin by itself has been found ineffective. Professor Kozhevnikov submitted a report which did not even mention penicillin. Professor Pashkov conceded that penicillin had been helpful in cases of congenital syphilis. In spite of their "old fashioned" treatment, the Russians maintained that syphilis was being eradicated by prompt medical care and improvement in living conditions, by elimination of unemployment, by elimination of prostitutes, and by big allocations (of funds) for needs of health protection and education.

Good sources of information on syphilis which appeared during the past year include the review by Wortmann,[14] covering the same period as our 20th annual review.[15] Willcox [16] has presented the eighth in a series of annual reviews of the world's literature on the venereal diseases, and Hasselmann [17] has prepared a detailed technical paper on the histopathology of pinta, yaws, and syphilis.

History of Syphilis

The history of syphilis, always of interest, was a feature of more than usual attention in this review period. Bloomfield [18] has prepared a bibliography of internal medicine (syphilis). Part I deals with the era from John Hunter to the discovery of the treponeme (1905). Part II contains material from the discovery of the spirochete. Mention has already been made of Cleugh's "Secret Enemy." [1] Fessler [19] described syphilophobia in the 17th century as based on the report of Wiseman. MacGregor [20] has outlined some 18th-century venereal disease publicity. Harrison [21] paid tribute to Neisser and to the Neisserian principles in venereology.

Paul Ehrlich. — Since no comprehensive biography of Paul Ehrlich has ever been written, the recent stimulating article by Hermann Pinkus [22] fills a great gap in medical history. To most of us, the name of Paul Ehrlich in connection with dermatosyphilology at once recalls his most impor-

tant practical achievement, the development and introduction of arsphenamine ("606" or Salvarsan). However, his other accomplishments are so numerous that we urge the reader to consult the original article, which in itself is a summary of the many contributions of this great figure.

Syphilis of Yesterday.—Carleton [23] has published his recollection of syphilis of yesterday. By yesterday, he means the early 1900's. Speaking from his own experiences, he describes the problem inherent in the diagnosis and the treatment of syphilis in those days, particularly as the description of chancre in the textbooks then available did not correspond to those seen by the doctors. The treatments he covers range from mercury ointment to arsphenamine, and he describes the first use of arsphenamine in America. Early attempts at prophylaxis during World War I are described also.

History of Neurosyphilis, Paresis.—Nicol [24] has reviewed the history of paresis from its original description by John Haslam, in 1798, to the present day. Initially mercury was used as treatment, then trivalent arsenicals, then tryparsamide, then bismuth, then fever therapy with erysipelas or injection of tuberculin, then malaria, and finally penicillin. The importance of follow-up observation throughout the life of the neurosyphilitic is emphasized.

As previously mentioned, the May, 1956, issue of the *A. M. A. Archives of Dermatology* was directed to the commemoration of the 50th anniversary of the Wassermann test. Although many of the papers are but indirectly related to the history of syphilis, the ensemble is analyzed here as a unit. The coverage includes many of the phases of the syphilis problem which have been discussed in these pages for a long time, as well as information on the most recent problems.

Significance of the Wassermann Test to Mankind.—The announcement of the test for the diagnosis of syphilis in 1906 by Wassermann, Neisser, and Bruck exerted such a profound effect upon mankind that the *A. M. A. Archives of Dermatology* deemed it altogether fitting to devote a special commemorative number to the occasion of the 50th anniversary of the Wassermann test. Accordingly, 17 articles, in addition to editorials, dealing with the direct effects of this discovery form the May (No. 5) issue of Volume 73 of the *A. M. A. Archives of Dermatology*, all of which may seem strange when one recalls that the name syphilology was recently dropped from the journal.

Cole [25] opens the commemoration with a fine toast. The progressive changes over a half century in the field of serodiagnosis of syphilis are completely reviewed by Hecht.[26] His discussion covers all the major variations in antigens, changes in technique of performance of the test, and the development of flocculation and verification tests. The mechanism and diagnostic value of all of the serologic tests for syphilis are briefly discussed by Kolmer.[27]

The influence of the Wassermann test on pregnancy and childbirth is discussed by Dennie,[28] while Stillians [29] recorded various opinions on neurosyphilis as they were expressed in the last 50 years. The decline in incidence of neurosyphilis is covered, as is a warning of possible flare-up. This threat is repeated in a broader sense by Schamberg,[6] who, as outlined above, feels that periodic epidemics of syphilis will continue unless and until immunization becomes a reality. Although the attack rate of syphilis in the United States has decreased 93% from 1947 to 1954, he does not believe that continued decline is assured. This decline resulted from cyclic change in incidence, coincidental administration of penicillin, and public health measures.

The various forms of ocular syphilis are reviewed by Klauder.[30] It is of interest that in congenital syphilis, the choroid and cornea are most susceptible to syphilitic involvement, with a frequency comparable to that of the osseous system. Whereas in acquired syphilis the iris is more susceptible, the choroid is considerably less so, and the cornea is rarely involved. He first observed

decline in incidence of syphilitic uveitis (iritis, cyclitis, iridocyclitis) about 1944 and subsequently its complete disappearance; the latter correlated the decline in incidence of early syphilis. Then, a gradual and progressive decline in incidence of patients with initial attacks of interstitial keratitis of congenital syphilis was observed. This decline began about 1946, seven years after enactment in Pennsylvania of the premarital examination law requiring an approved serologic test for syphilis and the prenatal examination law requiring such test of every pregnant woman. Klauder feels that in cases of ocular lesions of congenital syphilis there is a definite relation between the age of the patients and the year in which premarital and prenatal examination laws were enforced in the state of their birth.

The treatment of syphilis, from the time of the introduction of the Wassermann test to the present, the 50 years from 1906 to 1956, was discussed by several authors. The personal experiences of Harrison[31] in the management of venereal diseases for half a lifetime, were reprinted from *Medicine Illustrated*, Volume 3, (Nos. 7 and 8), July and August, 1949. The problems encountered in the treatment of syphilis in the arsphenamine era were reviewed by Rosen.[32] No discussion of antisyphilitic therapy is complete without mention of Jay Frank Schamberg,[33] whose biography, though presented briefly, clearly shows his tremendous influence in laying the foundations of chemical, chemotherapeutic, and dermatologic research in America.

The Cooperative Group Studies.—Prior to the introduction of penicillin, the recommendations of the Cooperative Clinical Group[34] established criteria of diagnosis, prognosis, and treatment which made for a uniform and intelligent approach toward syphilis control. This group came into existence in 1928. The cumulative material from the five participating clinics numbered something over 75,000 cases of all stages of syphilitic disease. The most widely accepted schedule of treatment was that of the Cooperative Clinical Group. This schedule required weekly injections for a period of one to two years, depending on the stage of the disease and the response to treatment. Although the therapeutic results of the Cooperative Clinical Group were eminently satisfactory, the treatment scheme had serious drawbacks, chief of which was the failure of patients to complete an adequate course of therapy because of its long duration; moreover, because of inadequate sterilization, new infections constantly appeared. Massive-dose arsenotherapy[35] was introduced to meet these criticisms of the older schedules. Today, one lesson of the "five-day" therapy remains, namely, biologic cure of syphilis can be achieved with short-term treatment with any effective drug, if the drug is given early in the course of the infection, for an adequate period of time, and in adequate dosage.

Some of the Early Phases of the Penicillin Therapy of Syphilis.—Shortly after massive arsenotheraphy was established, penicillin was introduced and now has completely eliminated the need for arsenicals. The clear-cut behavior pattern for short-term curative systems as observed with massive-dose arsenical therapy was again seen following intensive penicillin treatment of early syphilis. The responses to penicillin therapy as observed in the first cases so treated is well described by Mahoney.[36]

Intramuscular Oxytetracycline in the Treatment of Early Syphilis.—The newest effective form of therapy discussed in the *A. M. A. Archives of Dermatology* devoted to commemorating the 50th anniversary of the Wassermann test is intramuscular oxytetracycline. This was used to treat 16 cases of early syphilis, utilizing a total dosage of 4.0 gm. Baler[37] reported that the darkfield examinations became negative in from 20 to 53 hours after therapy was initiated. Out of 16 cases, 12 were successful responses and 4 were failures, as determined by an 8- to 16-month observation period. The drug was well tolerated by all patients. Although it produced some local muscle irritation, this was only minimal in the concentration used. There were no gastrointestinal

disturbances as are often associated with this agent. This might possibly be due to the low total dosage used and to the bypassing of the alimentary tract. Baler's report shows that intramuscular oxytetracycline is definitely of value in the treatment of early syphilis, but an increase in total dosage up to 6 or 8 gm. is recommended in the hope of reducing the failure rate.

Penicillin in Late Latent Syphilis.—Niedelman [38] studied the effect of penicillin therapy in the serologic reactions of 316 cases of late latent syphilis. He followed his patients for a minimum of one year or as long as three years after initial treatment, a time range which the reviewers consider much too brief.

More data derived from the Tuskegee Study are presented by Olansky and his coworkers.[39,40] Some of their conclusions were as follows: 1. In untreated syphilis, the percentage reversing to negative by the Kahn test was lowest in patients 25 to 39 years of age with syphilis of less than 15 years' duration, highest in patients 55 to 69 years of age with syphilis of 30 to 44 years' duration. 2. It is estimated that less than 50% of untreated syphilis in male Negroes will be detectable by the Kahn technique 30 years after infection. 3. There is no evidence to indicate that the treponemal immobilization test in untreated syphilis becomes nonreactive with the passage of time. 4. Twenty-seven per cent of patients with spontaneous serologic reversal had clinical manifestations of late syphilis. 5. There is variability in the pattern of seroreversal in untreated syphilis just as in treated syphilis.

Treponema Pallidum

Barrack [41] suggests that syphilis and yaws are one and the same disease. By its change of environment from a tropical zone to a temperate one and under the conditions existing in that new environment, syphilis became a venereal disease. However, under certain circumstances in which the living conditions are of a very low standard, syphilis can revert to its former state of being an infectious and contagious disease and not necessarily a venereal one. Further, he points out that the disease believed to be yaws, brought to the Americas from Africa, was really syphilis. The slaves that brought it were infected prior to or during the voyage to America.

Chambers [42] reviews the various systems of nomenclature which have been employed in yaws, and he points out the various defects. He then presents the following classification (which is reproduced here in an abbreviated form):

I. Herald lesion. This may be a papule, granuloma, or macule.

II. Secondary manifestation. These are due to hematogenically spread organisms. These secondary lesions may appear as

1. Macular lesions.
2. Folliculopapular lesions.
3. Papular or lichenoid lesions.
4. Frambesiomata, polypapillomata, or granulomata.
5. Bone lesions.
6. Dactylitis.
7. Palmar and/or plantar granuloma.
8. Palmar and/or plantar hyperkeratosis.

III. Tertiary (or late) manifestations. These seem to be the result of antibody-allergen response. These late manifestations may appear as

1. Nodular lesions; may ulcerate.
2. Ulcerative or granulomatous lesions.
3. Psoriasiform or scaling lesions.
4. Gumma; may ulcerate.
5. Juxta-articular nodules.
6. Goundou (a hyperplastic osteitis).
7. Gangosa.
8. Palmar and/or plantar keratodermia.

Electron Microscopic Studies of the Morphology of Pathogenic Spirochetes.—Swain [43] subjected Leptospira icterohaemorrhagiae (Wijnberg strain), T. pallidum, virulent and Nichols strain, Borrelia duttonii, and B. recurrentis to electron microscopy before, during, and after partial digestion by trypsin and/or pepsin. True flagella were not seen in T. pallidum. T.

pallidum was found to contain three fibrils which were instrumental in maintaining the shape of the spiral.

Establishment and Maintenance of the Nichols Strain of Virulent T. Pallidum in Rabbits in Warm Countries.—Chacko and his co-workers [44] reported that in the warm climate of Madras, India, without the use of air conditioning they are able to produce syphilitic orchitis in the rabbit following a 10-day incubation period, which supplies satisfactory antigen for the TPI test. With average minimum and maximum atmospheric temperatures of 24.7 C (76 F) and 33.4 C (92 F), the mean incubation period on intratesticular inoculation was 10.76 days. The authors emphasize that a potent inoculum containing at least 30,000,000 to 40,000,000 treponemes per milliliter is needed to achieve this short incubation period in a warm environment.

Experimental Syphilis

While there was not an abundance of papers on experimental syphilis issued during this review period, the two which are cited make up in quality what is lacking in quantity. Especially noteworthy is the study of inoculation syphilis in human volunteers by Magnuson, Thomas, Olansky, Kaplan, De Mello, and Cutler.[45]

Syphilis in Human Volunteers.—Magnuson et al.[45] described a study in which 62 human volunteers at Sing Sing Prison, Ossining, N. Y., were inoculated with virulent T. pallidum. The intracutaneous inoculation of four graded doses of virulent T. pallidum (Nichols' strain) into each of eight nonsyphilitic human volunteers gave a 50% infectious inoculum of approximately 57 organisms. The 50% infectious inoculum in rabbits given the same suspension was approximately 23 organisms. Thus, the Nichols' strain of T. pallidum has maintained a high degree of infectiousness for man. The intracutaneous and subcutaneous injection of 50,000,000 heat-killed T. pallidum produced an anamnestic rise in TPI antibodies in some patients previously treated for early syphilis but failed to produce significant increases in reagin titers. No changes in circulating antibodies were demonstrated in nonsyphilitic control patients given this same antigen. Fifty-four volunteers who had previous syphilis were inoculated intracutaneously at a single site with 100,000 virulent T. pallidum. All but five of these patients had had presumably adequate therapy for their earlier infection. Two of the treated patients had to be discarded from the study because they received penicillin before the results of challenge inoculation were known. The five patients with untreated latent syphilis showed no clinical or serologic response to challenge and are presumed to have been resistant to superinfection. Of 11 patients previously treated for proved or presumed early syphilis, 9 developed darkfield positive lesions, while 2 developed darkfield negative lesions. All responded with increased STS titers and were considered to have been infected by the virulent inoculation. Patients in this group developed reagin and TPI titer increases much more rapidly than did the nonsyphilitic controls. Of three patients previously treated for proved or presumed reinfection, one developed a darkfield positive lesion, another a darkfield negative lesion, both associated with increased STS titers. One patient showed no clinical or significant serologic response to challenge. Of 26 patients previously treated for proved or presumed late latent syphilis, 10 were considered to have been infected. One developed a darkfield positive lesion, nine, darkfield negative lesions, all with increased STS titers. One of the latter lesions was a gumma. Three patients developed darkfield negative lesions not associated with STS titer increases, while thirteen patients showed neither clinical nor serologic change. Among five patients treated for proved or presumed congenital syphilis, darkfield-positive lesions developed in one, three developed a darkfield-negative lesion associated with increase in serologic titer, one of which lesions was a gumma. One patient showed no clinical or serologic evidence of infec-

tion. Of two patients previously treated for asymptomatic CNS syphilis, one may have developed a CNS reinfection; the other showed no evidence of reinfection. Patients who had previously had syphilis differed from nonsyphilitic controls in their reaction to infection. In a general way, this reaction was influenced by the duration of their original infection prior to treatment, but there was considerable difference among individuals. There is some evidence to suggest that the administration of heat-killed T. pallidum may have produced a "booster" effect in the immunity of patients previously treated for syphilis. Because of the possible relationship of other variables, this finding requires further confirmation.

Experimental Prophylaxis.—Arnold and Cutler [46] reported briefly on an extensive study of the effect of many different local and systemic agents in the prophylaxis of experimental syphilis in the rabbit. No attempt was made to determine the relative effectiveness of the various prophylactic agents tested, but it was pointed out that locally applied solutions of Orvus (sodium salt of technical lauryl sulfate) and oxophenarsine (Mapharsen) and solutions of Fumerane (antiseptic) as well as parenteral injection of penicillin enjoyed a very high degree of effectiveness.

Active Immunization Against Syphilis.—Tani and his group [47] mixed syphilitic rabbit serums and syphilis spirochetes and injected the mixture into the peritoneal cavity of a normal guinea pig. Inhibition of motility of spirochetes occurred; the spirochetes then began to decrease in number and completely disappeared. This phenomenon was named "Pfeiffer's phenomenon of syphilis spirochetes." It might be considered as a type of in vivo TPI test. For readings, it is recommended that ascitic fluid be collected 30 minutes and 2 hours after inoculation. These investigators state that they have achieved some active immunization in rabbits against syphilis. They believe that one of the reasons for the failure of others in this regard is the use of too small quantity of spirochetes. When a total of 4,320,000,000 of antiformin-treated syphilis spirochetes were injected subcutaneously into rabbits, the rabbits given inoculations revealed 10 times greater resistance against the development of chancre on the 22d day after completion of the vaccination than the normal control rabbits.

Prognosis of Syphilis

A significant contribution to prognosis of syphilis is the Oslo Study of the Natural History of Untreated Syphilis. Gjestland,[49] in continuing the epidemiologic investigations of untreated syphilis begun by Boeck and Bruusgaard in Oslo, has compiled a work comprising some 500 pages, 83 tables, and 12 figures, with a 70-page annex. Between 1891 and 1910 Boeck hospitalized approximately 2000 patients with primary and secondary syphilis at the University Hospital of Oslo until lesions healed without treatment. During 1925, Bruusgaard attempted a follow-up of the patients. Gjestland followed 900 to 1100 of the original patients and analyzed the data. The general conclusions indicate that about one out of every four patients (23.6%) with untreated secondary syphilis developed clinical secondary relapse, with no appreciable difference between the sexes. There was no direct evidence that clinical secondary relapse following untreated secondary syphilis was of ominous prognostic importance in respect to development of late lesions. Benign tertiary syphilis occurred in about one out of every six patients (15.8%). There was more "benign" syphilis in women than in men. Neurosyphilis occurred in 6.5% of the patients. About twice as many men as women were so affected. Cardiovascular syphilis occurred in 1 out of every 10 patients (10.4%). Men were affected twice as often as women. Other late syphilis occurred in two of the cases; both women died from hepatic involvement. Syphilis was the cause of death in 1 out of every 10 patients (10.8%). Men died as the result of syphilis twice as often as females.

Since the patients came from a lower stratum of society, they were exposed to many other diseases. Syphilis does not kill except through the lethal effects of late manifestations. The problem of spontaneous cure is not answered by these data, but Gjestland believes the results add support to the correctness of Boeck's principles, subsequently supported by Gruusgaard. A critique of Gjestland's report may be found in the March 10, 1956, issue of the *British Medical Journal*.[50]

The Tuskegee study of untreated syphilis in the male Negro has already been mentioned.[39,40]

Diagnosis of Syphilis

Considerable data continue to accumulate on the diagnostic aspects of syphilis. While the greatest progress is being made in serodiagnosis, the clinical phases of syphilis have not been slighted to say the least.

Serodiagnosis

One would think that with the development of the so-called specific procedures there would be but little interest in the details of the routine serologic tests for the diagnosis of syphilis. Strangely enough, this is not the case. In this review period much attention has been given to reagins,[51] cardiolipin antigens, newer techniques for complement fixation, and biologic false-positive reactions.[52-55] The general interpretation of serologic reactions and the newer developments have been discussed by Chorpenning,[56] by Dasgupta,[57] by Rein and Reyn,[58] by Harris and Olansky,[59] and by Olansky and Price.[60] Moore,[55] in addition to his excellent discussion of the biologic false-positive reactors, has produced an outstanding example of modern code medical writing: "Chronic BFP Reactors and Their Relation to DGG, CVD, and SLE."

Significance of Hyperglobulinemia.—Feinstein and Petersdorf [61] analyzed a series of 394 patients with hyperglobulinemia. Of these, 268 patients had diseases generally associated with an elevated serum globulin. These diseases are listed as Laennec's cirrhosis; other liver disease; nonmetastatic carcinoma; metastatic carcinoma; multiple myeloma; lymphomas; collagen disease (acute rheumatic fever, acute glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis, periarteritis nodosa, scleroderma); sarcoidosis; chronic pulmonary disease; and infectious diseases (kala-azar, lymphogranuloma venereum, filariasis, leprosy, pneumonia, schistosomiasis, subacute bacterial endocarditis, syphilis, trichinosis, tuberculosis). In patients whose serum globulin was 5.0 gm. per 100 ml. or higher, over 90% had specific "hyperglobulinemic" disease; about half had either multiple myeloma, sarcoidosis, or collagen disease. In patients with only slightly elevated globulin values, half had a specific "hyperglobulinemic" disease.

Feinstein and Petersdorf [62] found that in 326 patients with hyperglobulinemia on whom serologic tests for syphilis were done, 296 were negative and 30 were positive. Of the 30 positive reactors, 13 had unequivocal evidence of syphilis, and another 4 had good evidence for the disease. Thirteen patients (4%) were considered false-positive or probable false-positive reactors. These 13 patients had a variety of diseases, and there appeared to be no correlation between the height of the globulin and the occurrence of the false reaction. Of 74 patients with hyperproteinemia, 4 had reactive STS. Of these four, two were probably false positive reactors, an incidence of 2.7% for false-positive results. This figure is higher than the normal occurrence rate frequently reported (1 biologic false-positive per 4000 persons).

Transmission of Blood and Serum Samples.—Until recently comparatively little attention has been paid to the problems arising from the transmission of blood and serum samples for serological testing. But the question has now acquired greater importance and urgency with the development of international parallel testing of sera and with the need to send sera for testing from

survey areas remote from laboratory facilities. Price[63] has summarized the results of various experiments to determine the effect of transport on blood and serum samples in transmission by post and by air, through hot, temperate, and cold climates. These have shown that time and temperature have a very considerable effect on the keeping qualities of whole blood and of serum and that preservatives can be useful, at least with sera. But they have also made it clear that the causes of infection and hemolysis of samples still require much study. Thought must also be given to the size, shape, and general construction of blood-sample containers if specimens are to arrive safely at their destination and if contamination is to be avoided.

Cardiolipin Antigens.—During the past seven years considerable progress has been realized in WHO's work on cardiolipin antigens.[64] International reference preparations of cardiolipin and of lecithins have been established and are available from the Statens Seruminstitut, Copenhagen. A description of cardiolipin and of lecithins is included in Volume II of the "Pharmacopoea Internationalis." A monograph was prepared by Dr. Pangborn and her associates and published by WHO. The purification of cardiolipin and the proof that this substance, when combined with purified lecithin and cholesterol in certain proportions, gives a valuable antigen were of the greatest importance in the progress toward good sensitivity and specificity. Work is now in progress on the establishment of international reference preparations of serums from syphilitics in the form of freeze-dried serums, with a view to obtaining a common yardstick for the comparison also of the reactivity of different serologic methods. Because of the importance of this problem to all interested in syphilology, some detail of the current research in cardiolipin antigens is given. Schmidt,[65-67] too, has continued his fundamental studies on cardiolipin antigen.

Cardiolipin Antigens. — Preparation and Chemical and Serological Control: In 1951 the first edition of a monograph on cardiolipin antigens was prepared for WHO by the Division of Laboratories and Research, New York State Department of Health, Albany, N. Y. Since that time several important developments have occurred and thus a new edition has become necessary.[68] Among these developments are progress in the purification of cardiolipin and simplified methods for complement fixation and calculation of the 50% units. The first two chapters, by Dr. Pangborn, cover in detail the methods of preparing the antigens (including the preliminary extraction of cardiolipin and lecithin from beef heart, the purification of cardiolipin, and the purification of lecithin, from both fresh eggs and beef heart) and the chemical analysis of the components of the antigens. The last chapter, written by the other four authors, deals with the serological examination of cardiolipin antigens, giving specific directions for determining the optimal proportions in which cardiolipin, lecithin, and cholesterol must be mixed to give acceptable sensitivity and specificity in particular serodiagnostic tests. There is also an annex on direct-probability sequential analysis. This monograph provides up-to-date information on the preparation and control of antigens which have done much to improve the sensitivity and specificity of serologic tests for the treponematoses. As the authors state, the changes in procedures in the new edition are "aimed primarily at simplification of the actual performance of the tests and of the evaluation of results, rather than at any important alteration in the results that would be obtained or in consequent decisions to accept or reject an antigen component in question." In view of the international importance of continuing the work initiated by the Health Organization of the League of Nations before the second World War on standardization of serological antigens and methods and the possibility of developing international reference standards of cardiolipin and purified lecithin, the World Health Or-

ganization took up this matter for study. The *ad hoc* Expert Committee on Venereal Diseases pointed out that WHO might encourage a wider use of cardiolipin antigens and considered that the whole subject should be studied by a specially competent committee. In 1949 the newly established Subcommittee on Serology and Laboratory Aspects of the Expert Committee on Venereal Infections stressed the necessity for stimulating production of cardiolipin antigens but observed that the technical difficulties encountered in their large-scale production restricted their availability. Meanwhile the New York State Department of Health, in order to secure the purity of cardiolipin products, had established, for noncommercial nonprofit purposes, a protective patent for the United States. The department suggested that WHO should supervise the international control of cardiolipin. At its second session, the subcommittee discussed arrangements for such international control and recommended that WHO collect and make available to health authorities and major laboratories technical information on the isolation, purification, and standardization methods for cardiolipin and lecithin and on the control of these products as a basis for the eventual establishment of international reference standards. WHO, through its Expert Committees on Biological Standardization and on the "Pharmacopoeia Internationalis" and the Subcommittee on Serology and Laboratory Aspects (of the Expert Committee on Venereal Infections and Treponematoses), is now engaged in this work. Provisional international reference preparations of cardiolipin and of lecithins were established in 1951 by the Expert Committee on Biological Standardization; in 1954 these were replaced by international reference preparations, which national laboratories may obtain from the Department of Biological Standards, Statens Seruminstitut, Copenhagen, Denmark.

The results of a previous investigation of the serological properties of synthetic L-α-dimyristoyl lecithin had indicated that this substance was unsuitable for use in the preparation of cardiolipin antigens, since the antigen solutions prepared with it were unstable and considered less sensitive than those prepared with the natural egg lecithin normally employed. However, in view of the desirability of using well-defined, synthetic products in the preparation of these serodiagnosic antigens, fresh experiments were carried out, using a new, crystalline sample of the synthetic lecithin in question.[69] As before, the antigens prepared with the synthetic lecithin were compared for sensitivity and stability with those prepared with natural egg lecithin. Antigen solutions containing either the synthetic or the natural lecithin were made up according to the formulae required for the Kline and Kolmer tests, the same batch of cardiolipin and the same preparation of cholesterol being used in all solutions. Over a period of six months 157 sera (or dilutions of sera) from syphilitic patients and 56 sera from nonsyphilitic persons were subjected to the Kline and Kolmer tests. The results showed that the antigen solutions containing the synthetic lecithin were slightly less sensitive than those containing the egg lecithin, but that this decrease in sensitivity was very much less marked than that observed previously in the case of the noncrystalline L-α-dimyristoyl lecithin. To test stability, the various antigen solutions were stored at room temperature in the laboratory for periods of three weeks and two, three, and five months. It was found that the serological properties of all the solutions remained unimpaired during storage. It would thus appear that synthetic, crystalline L-α-dimyristoyl lecithin can be used satisfactorily in place of natural egg lecithin in the preparation of cardiolipin antigen. Reyn and Bentzon [70] showed that synthetic, crystalline, L-α-dimyristoyl lecithin could replace natural lecithin in the preparation of cardiolipin antigens, but that the antigens prepared with the synthetic lecithin were significantly less sensitive than those prepared with an equimolar amount of natural lecithin. The authors consider that further investigation

is required before the use of synthetic lecithin is finally adopted.[71-73]

Kline's [74] continued studies, however, indicate that the use of pure crystallized synthetic L-α-dimyristoyl not only simplifies the preparation of an optimal antigen emulsion for the detection of syphilitic reagin, but also improves its quality. Tonks and Allen [75] used pure unsaturated individual lecithin L-α-(dipalmitoleyl) lecithin as a component in cardiolipin antigens for the VDRL microflocculation test and the Kolmer complement-fixation test for syphilis, and obtained promising results. A pure saturated lecithin, L-α-(dipalmitoyl) lecithin, prepared from the unsaturated forms above by hydrogenation was also tested. Antigens containing it were successfully used in the Kolmer test but showed little or no reactivity in the VDRL test.

Comparative Studies on Lecithin as a Component of Cardiolipin Antigens.—In a report from four laboratories [76]—at Albany, N. Y. (United States), Bergen (Norway), Naples (Italy), and Tel Aviv (Israel)—of the results of comparisons between egg-yolk lecithin and lecithin of beef-heart origin it was shown that in complement-fixation tests there is good agreement between antigens prepared with egg-yolk or beef-heart lecithins. In slide precipitation tests, one laboratory, using the rapid Rein test and the rapid Rein test with stained antigen, reported that egg lecithin gave stronger reactions than those with beef lecithin and considered that the comparison required repetition. A second laboratory which performed the microscopic slide precipitation test reported comparable results with both types of lecithin. However, in precipitation tests, the results are as yet incompletely documented, although personal communications to us from American serologists show that the Hinton, VDRL, and Kline procedures give comparable results for both types of lecithin. Since the last two mentioned are not of fixed composition with respect to lecithin, our opinion of these tests is that comparable levels of reactivity are attained within the accustomed range of lecithin concentration.

Evaluation of Cardiolipin Antigen in Routine Wassermann Reactions.—Based on a comparison of cardiolipin and standard antigens in over 7000 complement fixation tests, Shaw [77] found that cardiolipin gave increased sensitivity but loss of specificity. Nonspecific reactions were particularly evident with antenatal serum.

Effect of Some Anticoagulants upon Serodiagnostic Tests for Syphilis.—Coleman, Appleman, and Kurtz [78] stated that the level of reagin antibodies of syphilis as measured by the standard Kahn, Mazzini, VDRL slide, and Kolmer tests in blood treated with heparin, sodium citrate, thymol-fluoride mixture, and potassium-ammonium oxalate mixture has been shown to be equivalent to that in serum. The addition of these anticoagulants appears to make the flocculation tests slightly more sensitive. The completion of the clotting mechanism is not required for the release of these antibodies. Some of the anticoagulants destroy complement to a small but capricious degree.

New Techniques for Complement-Fixation Tests.—Roulin [79] described a new technique for the serodiagnosis of syphilis by the complement-fixation test. The method involves the use of increasing doses of complement, namely, 0.20 ml. and 0.30 ml. of a 1/40 dilution. No special material or reagent is required. Fixation, which is prolonged, takes place at low temperature, and titration to determine the necessary sensitization of the red blood cells is carried out in a single operation. In considering the specificity and sensitivity of the technique the author reports that specificity is at least equal to that of the Kolmer test and greater than that of the flocculation reactions in the Kahn standard, the Meinicke clarification, and the Kline tests. The sensitivity of the technique is based on comparison of the quantitative and qualitative results with those obtained in the Meinicke clarification, Kahn standard, VDRL, Debains, and Kolmer tests.

For quantitative reactions, the only modification is the substitution for the serum of an equal quantity of the successive dilutions. Tables show a clear difference in sensitivity which appears to favor the technique reported. The possible reasons for this greater sensitivity are discussed. It is believed that it is related to use of small quantities of complement, which considerably increases the ratio of suspect serum to complement. (For details of the technique, it is necessary to read the original paper.)

Muschel and Lowe [80] described a new method for performing the complement fixation test in which no spectrophotometer is required. Neither instrumentation nor mathematics need deter the use of a precise standardization of complement. The cardiolipin antigen and complement amounts have been changed so that the procedure is set at a lower reactivity level. A simplified method has resulted by substituting a two-tube test for the four-tube test. All serum specimens tested by this procedure were also tested by the cardiolipin microflocculation test of the U. S. Army and Air Force. There was complete agreement between the two tests in 87% of the serums and partial agreement in 10%. This new procedure is a practical, simple, and reproducible one.

Anticomplementary Reactions in Syphilis.—Rappaport and Stark [81] confirmed Lighter's 1953 observation that sera from patients suffering from congenital syphilis were responsible for anticomplementary reactions about seven times more often than would be expected were anticomplementary reactions distributed among sera from patients with congenital syphilis and those with acquired syphilis. They inferred from their experimental study of this problem that the agent which removed the complement in the control tube was actually fixed by syphilitic antigen, or by a substance which behaved serologically like syphilitic antigen, the presence of this antigen in the serum causing it to be anticomplementary.

Comparative Study of Rein-Bossak Test with Kahn, Kolmer, and VDRL Tests.—Rein-Bossak, Kahn, Kolmer, and VDRL tests were performed at the Manila Public Health Laboratory on 6540 serums.[82] Results are given only in terms of complete and partial agreement and disagreement; the source of the serums is not given. No attempt is made to compare specificity and sensitivity. The highest percentage of complete agreement occurred between the VDRL and Kolmer tests (95.13%), and the next highest percentage of complete agreement occurred between the Rein-Bossak and Kolmer tests (93.97%). The greatest percentage of complete disagreement was between Kolmer and Kahn tests; next greatest, between Rein-Bossak and Kahn tests. The findings are discussed.

Value of Kahn Test in Africans.—In an effort to evaluate STS in Africans, Evans [83] presents a lengthy and discursive paper. Of 6006 patients in whom the Kahn test was performed, there were 28% positive reactions, 21% weakly positive reactions, and 51% negative reactions. In 1889 seroreactive patients without clinical evidence of syphilis or the other treponematoses an attempt was made to decide whether or not syphilis was present on the basis of history of genital lesions; genital scars; discovery of congenitally syphilitic children; syphilitic status of sexual partner; history of repeated abortions, miscarriages, and stillbirths, and other factors. On the basis of far from conclusive evidence, the author felt that biologic false-positive reactions accounted for between 9% and 17½% of the seroreactions in this group without clinical evidence of disease. Of interest is the study of 137 patients with positive blood smears for malaria (Plasmodium falciparum). Twenty-seven per cent were found seroreactive. A close parallel was noted between the monthly variations of malaria and the incidence of seropositivity. The fact that 37% of the children, but only 23% of the adults, were seroreactive is explained by the author by the statement that biologic false-positive reactivity due to malaria is most likely to occur early in the course of the

disease. Kahn tests performed on 477 lepers in two leper colonies gave only 18.4% seropositive results. Seropositivity was most frequent in the lepromatous type, least in the tuberculoid.

Transient Seropositive Nonsyphilitic Pneumopathies (Fanconi-Hegglin Syndrome).—The Fanconi-Hegglin syndrome consists of bronchopulmonary symptoms, roentgen signs of pulmonary inflammation with perihilar infiltration, and a positive Wassermann reaction in nonsyphilitic persons. All the symptoms and signs disappear together with the rapid reversibility of the reaction for syphilis. In a report by Cerviá and Méndez de Lugo[84] the disease developed in the course of an epidemic bronchopulmonary disease. The patient had no syphilis but did have healed pulmonary tuberculosis. The clinical symptoms, roentgen signs, and positive results of the Meinicke and Sachs-Witebsky reaction reverted to negative within a week from first consultation. The treatment during this week consisted of administration of penicillin in daily doses of 800,000 units, 0.5 gm. of streptomycin, and 1 gm. of ascorbic acid. The reaction for syphilis continued negative for the three weeks the patient was under observation, after it had reverted from a week of positive results. Although the syndrome is benign, it has a medicosocial significance. It lasts for three to six weeks. The false-positive results of the reactions for syphilis are due to the dysproteinemia of the globulin fraction that, latent or evident, exists in certain types of pulmonary inflammation and manifests itself by transient changes of the blood serum that are favorable for the production of the false-positive test for syphilis.

Serological Findings in Leprosy and Tuberculosis with the Wassermann, Meinicke, and VDRL Tests.—In the course of a WHO-assisted venereal disease control program in 1952 in Egypt, 820 cases of leprosy and 720 cases of tuberculosis were serologically examined by Ruge,[85] with the Wassermann, Meinicke (MKR II), and VDRL tests. The sera were collected at random from all patients at the Abou Zabal Hospital Leper Colony and from patients who came for treatment in a number of outpatient clinics. All patients were thus under medical supervision and treatment. On serological and anamnestic evidence, 31 cases of syphilis were discovered among the leprosy patients and 37 among the tuberculosis cases. Apparently false-positive reactions were seen in 203 leprosy cases (25%) and in 38 persons with tuberculosis (5%). The probability that a fairly high proportion of these reactions were in fact caused by otherwise undetected syphilis or were nonspecific is discussed. Of the three tests employed, the Meinicke was the most specific, followed in decreasing order by the Wassermann and the VDRL tests. Syphilis was more frequent among males with tuberculosis than among those with leprosy, and this is attributed to the fact that the latter are kept in greater isolation. However, the author points out that it is less easy to explain the findings of more syphilitic females than males among the leprosy patients, while in tuberculous persons the difference in syphilis incidence between males and females was not very great.

Treponemal Immobilization Test and Other New Tests

Gradually the exact status of the treponemal immobilization test (TPI) is being established. Evaluation studies continue to attest to the value of this procedure in the diagnosis of syphilis in general[86-89]; of syphilis in pregnancy[90,91]; of latent syphilis.[92] Ledbetter,[93] after applying the T. pallidum immobilization test to 4462 serums representing 2545 patients with or without syphilis, believes the TPI test has its greatest value as a verification test. It enables the clinician to distinguish between biological false-positive reactions and true-positive (syphilitic) reactions in standard serologic tests. Also, the TPI test eliminates false-negative reactions. It is of little value to the clinician as a criterion for cure.

TPI Test in Cardiovascular Syphilis.—Friedman and Olansky [94] reported observations on TPI tests in 33 persons with lesions of the aorta or aortic valves and in whom standard serologic tests for syphilis were either nonreactive or weakly reactive. In a group of 12 patients thought to be syphilitic, the TPI tests were reactive in 9 and nonreactive in 3. In a group whose disease was judged clinically to be nonsyphilitic in origin, no reactive TPI results were found. In a group of nine cases with aortic valvular lesions of uncertain etiology, four had reactive and five, nonreactive TPI tests. None of the four patients with demonstrable immobilizing antibody had clinical evidence of syphilis by history, commonly used serologic tests for syphilis, or physical signs apart from the aortic insufficiency. Treponemal immobilizing antibody was detected in the blood of reagin-free subjects with late manifestations of cardiovascular syphilis 26 to 43 years following the initial infection. The treponemal immobilization test is of definite help in establishing the existence of syphilis in persons with negative serologic tests commonly employed. A large margin of error may attend the diagnosis of cardiovascular syphilis in patients in the absence of collateral evidence of syphilitic infection.

TPI Test in Negroes.—Pagès, Pédoya, and Girard [95] discuss the high seropositivity rate in the Negro and point out that many French workers feel that seroreactions in the Negro are nonspecific and are due to constitutional or ethnic factors. In an attempt to test this hypothesis, the authors performed TPI tests on 36 seropositive Negroes. In 33 the TPI test was positive. They conclude that seropositivity in the Negro is usually specific and due, in their series of cases, either to syphilis or yaws.

Reproducibility and Specificity of the TPI Test.—Sequeira and Wilkinson [96] examined the behavior of the TPI test with nonsyphilitic sera to establish the criteria of negativity and its specificity. The conclusions reached, applied to routine sera, are as follows: The reproducibility of the TPI test from a laboratory aspect and in routine use is comparable to that of the STS. While there are as yet insufficient reports of results on nonsyphilitic sera for an absolute assessment of specificity, the results so far available indicate that the TPI is highly specific for the treponematoses. It appears likely that a proportion of patients with negative STS and positive TPI may represent a form of latent syphilis.

Laboratory Aspects of TPI Test.—Continued attempts to improve the TPI test technically are being made.[97,98] At the Venereal Disease Research Laboratory, Harris and his group [98] made alterations in procedures in the TPI test during the past year in order to overcome the following difficulties: Slowly developing orchitis (more than 10 days); low treponeme count in testicular extractions; occasional survival failures in one or more tubes of controls; large percentage of inconclusive results, and unsatisfactory bovine albumin for the survival medium. The alterations were as follows: The rabbits were kept for at least 30 days before use to allow elimination of antibiotics they might have received with feed; only nonreactive (TPI) rabbits were used; treponeme suspensions used for rabbit inoculation were taken from rabbit testes which were inoculated not more than 11 days previously; 0.5 ml. of treponeme suspension containing not less than 2.5×10^7 treponemes per milliter were inoculated into the rabbit testes; these testes were removed not later than 10 days after inoculation for use in the TPI test; control survival failure was eliminated by changing the method used for cleaning glassware and the method for handling guinea pigs; the insoluble portion of the bovine albumin was removed before mixing with the other ingredients of the medium; inconclusive results were almost eliminated by immediately stoppering the tubes as soon as the blood was drawn or by using paraffin-coated cork stoppers. These and other changes in the method of carrying out the TPI test are discussed.

Treponemal Agglutination Test.—Although the treponemal agglutination test (TPA) seemed to hold much promise, the amount of work published on this procedure is not entirely definitive.

Rein [99] editorially stated that with a continued decrease in the incidence of syphilis there will be a relative increase of BFP reactors among seropositive persons. He states that about 40% of white persons in upper socioeconomic and educational levels who are routinely discovered to have positive standard serologic tests for syphilis in the absence of any clinical or anamnestic evidence of syphilis or in the absence of reasonable opportunity for infection do not have syphilis and give BFP reactions. Therefore, it is of utmost importance that a specific test employing antigens of T. pallidum be made available to the physician who is frequently faced with the problem of deciding which of his seropositive reactors have syphilis and which are chronic BFP reactors. Newer tests of T. pallidum immune adherence (TPIA) and T. pallidum agglutination (TPA) are being found to be more practical and more feasible than the T. pallidum immobilization (TPI) test. Since killed treponemes are used, the antigen can be refrigerated for months and can be made available to those laboratories which do not at present have adequate facilities to cope with the technical complications of the TPI test. In the annotations section, *Lancet* [100] states that a treponemal agglutination test holds great promise. Work done on this test by several of those interested in this field is mentioned. The impression given is that further research, which is in progress, is necessary before this test can be used routinely. Ehrmann and Nielsen [101] reported upon the results of a T. pallidum agglutination test using heat-killed pathogenic treponemes in 154 human and 40 rabbit sera. Comparison with tests for reagin and the TPI test were carried out on all specimens. The TPA test was similar to the TPI and superior to reagin tests in presumably biologically false-positive sera. However, agglutination occurred with sera from patients with rheumatoid arthritis and lupus erythematosus. The authors considered this nonspecific and due to an agglutinating factor found in these diseases. In syphilitic rabbits, agglutinins appeared almost simultaneously with reagins and earlier than immobilizing antibodies. The authors conclude that the TPA test in its present form is unsatisfactory as a diagnostic test, primarily because of a lack of specificity. Since the agglutination test seems to have a definite place in serology because of its ease of performance and clear-cut results, attempts were made by Cain and Watson [102] to make it more suitable for use in the small laboratory and clinical center. First, the test was performed at room temperature and found to be valid. Then, in validation of the antigen, the time criterion was reduced from 24 to 8 hours. Cortisone was substituted for X-irradiation to inhibit the antibody-forming mechanism of rabbits in order to permit the harvesting of an antibody-free antigen. Barbital (Veronal) buffer was found to be suitable replacement for the more complicated basal medium. Penicillin was found to be satisfactory as an inactivant in place of heat. Magnuson and McLeod [103] found that one approach to obviating some of the difficulties and complexities of the TPI test is in the use of T. pallidum as an antigen in agglutination tests. The four main representative techniques of such tests are compared with respect to strain of organism used, treatment of rabbits, time of harvesting, extracting medium, method of inactivation, preservative, and reagent. The results obtained with the different techniques are then reviewed, and the various difficulties met in each are discussed. They believe that the T. pallidum agglutination tests do not yet have the diagnostic value equal to that of the TPI; the technical difficulties have not yet been overcome, and the immunological interpretation of results is by no means clear. Much still has to be done, and indeed it is possible that entirely different methods may even supersede techniques using whole, virulent T. pallidum as antigen. Along these

lines, in studies conducted at the International Treponematoses Laboratory, Department of Microbiology, The Johns Hopkins University, Baltimore, Hardy and Nell [104] devised a method for the preparation of T. pallidum suspensions that can be used for specific agglutination studies and can be stored for months at 4 C without loss of agglutinability. These suspensions react with two distinct antibodies in syphilitic human serums: Wassermann antibody and specific treponema agglutinin (STA). The agglutination of treponemes by STA is enhanced by heat treatment and by aging of the suspension and is inhibited by a divalent cation, probably Ca++, normally present in serum. This inhibition can be eliminated by the use of a chelating agent, ethylenediaminetetraacetate. From these findings the authors devised a simple agglutination test for treponemes that is highly specific and is very sensitive. The test was tried on 430 serums, of which 116 were from patients with diseases other than syphilis or from normal persons, 58 from biologic false-positive reactors (BFP), and 256 from patients with various stages of syphilis. Comparative tests were made with the TPI and the standard serologic tests on 302 serums, 244 syphilitic and 58 BFP's. The results of the agglutination test agreed with those of the TPI test in all but 20 of the serums. The instances of discrepancy are discussed. These results are further compared with agglutination tests carried out before and after absorption with VDRL antigen.

T. Pallidum Complement-Fixation Test (TPCF).—Portnoy and Magnuson [105,106] describe the preparation of an antigen from virulent T. pallidum by removing lipid fractions and then extracting the antigenic material by a solution containing sodium desoxycholate, sodium citrate, and sodium chloride. The resulting antigen is used in a complement-fixation test (TPCF). Modestly, the authors state that preliminary results suggest that the test may be of value in the diagnosis of syphilis. Antigen lots have shown excellent reproducibility as measured by serologic behavior, and the measurement of TPCF antibody has likewise been found to be highly reproducible. The separate identity of TPCF antibody from TPI antibody and reagin is suggested by absorption, inhibition, and correlation studies. Concerning specificity, 98% of 383 nonreactive STS cases were negative in the TPCF. Of the eight cases negative with STS and reactive with TPCF, four were reactive with TPI. In a presumed biologic false-positive group of 49 cases, the TPCF showed 92% agreement with the TPI, suggesting a high specificity for the TPCF. In primary and secondary syphilis, the TPCF and STS showed equal percentages of reactivity, whereas the TPI gave a lower incidence of reactions. However, in presumed latent and late syphilis, the TPCF showed a lower incidence of reactions as compared to both TPI and STS. The significance of the lowered incidence of positive reactions in presumed latent and late syphilis with TPCF is not known at present.

Magnuson and Portnoy [107] report briefly on the status of the T. pallidum complement fixation test (TPCF). In principle the test is simple. Virulent T. pallidum are obtained from infected rabbit testes. By differential centrifugation the treponemes are concentrated, the lipid fractions removed by successive acetone and ether extractions, and the active protein-like antigen is then removed from the dried treponemes by a 0.2% solution of sodium desoxycholate. The resultant antigen is employed in a conventional complement-fixation test. In primary and secondary syphilis the TPCF is somewhat more reactive than the TPI test. In central nervous system syphilis, including tabes dorsalis, the TPI was more reactive. In congenital syphilis, a slight advantage went to the TPCF test. In latent and cardiovascular syphilis, the two treponemal tests appear to be about equally sensitive. In a group of 26 patients in whom the differential diagnosis lay between biologic false-positive STS and latent syphilis, the STS, TPI, and TPCF results agreed in

only 33.5%. However, the TPI and TPCF results were in agreement 94% of the time. In 78 patients who were submitted as "definite" biologic false-positive reactors, TPI and TPCF tests agreed in all but 1, or 98.7% of the time. Two commercial manufacturers are beginning the production of TPCF antigen. If the present trends continue, such production will make it possible for the well-run serologic laboratory to perform these tests.

Immune Adherence Test.—Daguet [108] described a number of variants of the T. pallidum adherence-disappearance reaction, which is carried out in two stages: first, immune adherence of sensitized treponemes to normal red blood cells and, secondly, disappearance of the antigen by leucocytic phagocytosis. The immune adherence phenomenon by itself can be used for the detection of specific antibody. Absorption experiments have shown that this antibody is different from the Wassermann reagin and closely allied to the immobilizing antibody of the TPI test. The results obtained with the adherence-disappearance reaction on 914 sera examined by three groups of research workers showed that of 382 sera of proved nonsyphilitics (TPI negative), only 1 serum gave an adherence-disappearance reaction, while with 307 sera of untreated syphilitics (TPI positive) only 7 failed to react. There are still numerous problems to be solved—those, for instance, of treponeme counts, spontaneous disappearance, lack of reactivity, antigen preparation, and criteria of positivity and negativity— but the reaction nevertheless presents even now certain advantages over the TPI test. Thus, it is possible to use suspensions of killed treponemes as antigen, eliminating the risks inherent in the use of the live organism, and the reaction takes place in a very brief space of time, allowing numerous sera to be examined in a few hours. The procedure, moreover, is relatively inexpensive, only 1 ml. of antigen being necessary for each serum under test and 100 ml. of antigen being obtainable from the irradiated testicles of a single rabbit.

Lamanna and Hollander [109] demonstrate that the spirochetal "immune adherence" (Nelson) with human red cells is merely a particular case of a general phenomenon, namely, adhesion of the Rieckenberg type.

Cerebrospinal Fluid

Post-Lumbar-Puncture Reactions.—Since the reactions following diagnostic lumbar puncture are probably due to the same factors as those producing sequellae subsequent to spinal anesthesia, the report of Vandam and Dripps [110] should be considered here. They observed an over-all incidence of headache in 11% of their patients. The oldest patients were least susceptible to headache, and men were less susceptible than women. Its incidence when needles of small diameter were used was much less than with needles of large diameter; the 22-gauge needle was found best for routine use. Headache could be virtually eliminated by the employment of a 24-gauge needle. Vandam and Dripps feel that their data on duration and time of onset of the headache, on the effects of postural changes, and on the visual and auditory phenomena indicate that this syndrome results from a decrease in cerebrospinal fluid pressure and that the decrease is caused by leakage of the fluid.

TPI Test on Spinal Fluid.—Miller and his co-workers [111] studied the TPI test on 376 specimens of spinal fluid obtained from 324 patients. Of 100 patients given a diagnosis of neurosyphilis, there were 14 with negative immobilization tests on the spinal fluid. This is a discrepancy of 14% for the immobilization test compared with the clinical diagnosis. In the same series of 100 patients, there were 16 cases in which the standard test on the spinal fluid was negative, or a percentage of discrepancy of 16 for the standard test compared with clinical diagnosis. It is well known that a negative standard test on a spinal fluid can not be interpreted as ruling out the diagnosis of neurosyphilis. On the other hand, the group felt that positive immobilization tests on the spinal fluid are diagnostic

of neurosyphilis. Levels of immobilizing antibody in the spinal fluid were in general significantly lower than in the blood. The ratio of the immobilizing antibody in spinal fluid to that in blood varied from a minimum of 1:1.6 to a maximum of 1:113. The maximum effective dilution in spinal fluid was 1:74, while in blood it was 1:2, 150. Zellmann and Lutz [112] also reported experience with the TPI test in the cerebrospinal fluid of 43 patients with early syphilis, latent syphilis, neurosyphilis, and biologic false-positive reactions. The behavior of TPI antibody in the central nervous system appears to be similar to that of reagin. In latent syphilis there is disagreement between the two tests in that there are patients with latent syphilis who have the TPI antibody in otherwise normal spinal fluids. It is probable that patients with latent syphilis who have demonstrable TPI antibody in the cerebrospinal fluid may be reclassified as a type of symptomatic neurosyphilis. Three patients presented chronic biologic false-positive reactions in both blood and spinal fluid. Zellman, and Lutz postulate that alterations in the globulin fraction of the spinal fluid probably secondary to tissue injury are responsible for the false-positive reactions, since these patients had brain tumor, probable collagen disease, and probable sarcoidosis, respectively.

(To be concluded)

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Case Reports

Amelioration of Diabetes Mellitus Due to Pituitary Necrosis

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The mutually antagonistic action of insulin and of a hormone produced by the anterior pituitary gland was demonstrated by experimental work reported by Houssay and Biasotti in 1931. These workers found that the diabetes observed in hypophysectomized-depancreatized dogs was much less severe than was that seen in dogs in which the pancreas alone had been removed.[1] As contrasted to the depancreatized dogs, the hypophysectomized-depancreatized animals displayed a relative drop in blood sugar level, a trend toward spontaneous hypoglycemia with fasting, a slight decrease in nitrogen excretion, an absence of ketosis, and a survival of several months' duration without insulin. Subsequent investigations revealed this phenomenon to occur in various other mammals and in amphibians as well.[2]

This phenomenon, which has become known as the Houssay phenomenon, has been observed rarely in man. In a recent review of the literature, Harvey and de Klerk found only 11 previously reported cases, to which they added an additional three cases.[3] Infarction of the pituitary gland due to arterial thrombosis has been the commonest etiological factor found at autopsy. Four cases of this sort have been described occurring in association with postpartum hemorrhage. The phenomenon has also been reported due to involvement of the pituitary with sarcoidosis and due to abscess formation within the gland.[3-7] A recently observed case in which sudden amelioration of diabetes mellitus occurred in association with pituitary necrosis secondary to metastatic carcinoma is described.

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Report of Case

The patient was a 60-year-old white man, a merchant seaman, admitted to the hospital on Oct. 6, 1954, with a chief complaint of multiple ulcerations of the legs. Past history indicated that a diagnosis of diabetes mellitus had been established eight years previously but that dietary and insulin management had been poor. Seven years previously surgery had been performed at another hospital for neoplastic disease of the larynx, the procedure apparently being limited to a resection of the true vocal cords. The patient also gave a history of chronic bronchial asthma. He had recently noted an increase in symptoms, and at the time of admission he complained of dyspnea and wheezing.

Physical examination showed a moderately obese, well-developed, somewhat lethargic white man of stated age in moderate respiratory distress. There was a low-grade fever. Eye examination showed that bilateral iridectomies and lens extractions had been performed in the past. A healed surgical scar was present over the trachea. The anteroposterior diameter of the chest was increased, and wheezes and rhonchi were heard bilaterally on auscultation. Examination of the heart revealed a regular rhythm, with a rate of 120 per minute. There was no cardiac enlargement to percussion or to palpation. The liver was slightly enlarged. A mild cyanosis of the nail beds was present. A stasis dermatitis with ulcerations involved the lower portions of both legs.

Laboratory examination on admission revealed a blood sugar of 247 mg. per 100 cc. and 4+ glycosuria. X-ray of the chest showed evidence of linear atelectasis in both lower lobes. Skull x-rays were normal.

Shortly after admission, the venous pressure was measured to be 260 mm. of saline. The arm-to-tongue circulation time with dehydrocholic acid (Decholin) was 15 seconds. Therapy was instituted with the use of bronchodilators, antibiotics, digitalis, and crystalline insulin. Local therapy was given to the ulcerative lesions on the legs. The patient's general condition rapidly improved, but management of his diabetes was difficult, large dosages of crystalline insulin being required over a prolonged period of time.

In December, 1954, a small hard indurated mass was found in the right anterior cervical area. On direct laryngeal examination the area of the posterior false cords was suspicious, and a biopsy revealed squamous-cell carcinoma. Irradiation therapy was given to the neck, with follow-up examinations showing no apparent evidence of any local tumor residual. During this period diabetic control remained erratic, with frequent glycosuria and with blood sugars as high as 290 mg. per 100 cc. on occasion. Subsequent to irradiation therapy, however, it was possible to obtain better regulation with very rigid dietary management in conjunction with 25 units of protamine zinc insulin mixed with 40 units of crystalline insulin given each morning. Thereafter, glycosuria was infrequent, and fasting blood sugars averaged about 140 mg. per 100 cc.

In September, 1955, the patient complained of pain in the left shoulder, and x-rays revealed tumor metastases in the left humerus and scapula. This was followed by a gradual deterioration in the patient's general condition. On Nov. 1, 1955, he was observed to be weak and sweaty, and it was felt that he was experiencing mild hypoglycemic symptoms. For this reason intravenous dextrose infusions were begun, and long-acting insulin was discontinued. Crystalline insulin was ordered to be given according to the degree of glycosuria found on fractional urinalyses. Despite an adequate food intake, urinalyses performed every four hours for the next four and one-half days revealed no glycosuria, and no further insulin was required. The blood sugar on Nov. 1, 1955, was 100 mg. per 100 cc., and on Nov. 3, 1955, was 118 mg. per 100 cc. Skull x-rays on Nov. 3, 1955, revealed multiple skull metastases. Although the appearance of the sella turcica was normal, the clinical diagnosis of anterior pituitary insufficiency due to metastatic carcinoma was proposed. On the evening of Nov. 5, 1955, the patient became comatose and after several hours died.

A postmortem examination was performed. Gross examination revealed generalized carcinomatosis. The scalp, skull, dura mater, and pituitary were grossly involved. Small tumor metastases were found in the liver, heart, kidneys, cerebral cortex, and adrenal medullae, but without derangement of the gross architecture of these structures.

On microscopic examination, residual squamous-cell carcinoma was found in the larynx. Sections of the pituitary revealed that gland to be surrounded by metastatic carcinoma without actual invasion of the gland itself. A large portion of the gland, however, was found to be necrotic, this finding thought to be due to embarrassment of blood supply by the surrounding tumor. It was postulated that this might have occurred either from mechanical compression of nutrient arteries by the tumor or from actual infiltration of the tumor into the vessel walls with thrombosis. The examination of the adrenals showed tumor involvement of the medullae bilaterally, with early invasion of the cortices. There was also microscopic evidence of tumor invasion of the thyroid. An increase in fibrous tissue proliferation was seen within the pancreas, with a decrease in the number of islets of Langerhans and with shrunken and pyknotic β-cells within the islets.

Comment

The exact nature of the diabetogenic hormone of the anterior pituitary and the mechanism of its influence on carbohydrate metabolism remain uncertain. There appears to be a close relation between this hormone and the growth hormone of the same gland. Observations by Houssay and by Soskin and co-workers indicate that the diabetogenic effect occurs at the liver with an increase in gluconeogenesis from noncarbohydrates.[2,8] Reports by other investigators, however, favor an inhibitory influence on glucose utilization in the extrahepatic tissues.[9] The hormones elaborated by the thyroid and the adrenal cortex also influence carbohydrate metabolism, and observations by Wells and Kendall indicate that the influence of the anterior pituitary may be at least in part exerted through these glands.[10]

In the case reported, small adrenal cortex and thyroid metastases were present, but the gross architecture of these glands was not disturbed. It appears that the sudden drop in insulin requirement resulted from acute necrosis of the anterior pituitary and that this case represents another example of the Houssay phenomenon occurring in man. The necrosis in this case presumably occurred secondary to involvement of the blood supply of the gland by metastatic carcinoma.

Despite the infrequent reports of the occurrence of this phenomenon, it would appear that diabetic patients might be particularly susceptible to its occurrence because

of the frequent association of diabetes mellitus with vascular disease. Hypoglycemia in a diabetic patient who has been previously well controlled should cause this possibility to be considered. Necrosis of the anterior pituitary in itself is not fatal, and the prognosis of such patients should be greatly improved by replacement hormonal therapy and dietary measures.

Summary

The case of a patient with diabetes mellitus and with terminal amelioration of the disease with sudden drop in insulin requirement is reported.

Clinical and autopsy evidence indicates that this case is an example of the Houssay phenomenon occurring in man.

It is of importance to recognize the occurrence of this situation in cases more hopeful than the one described because of the excellent results that might be obtained from replacement hormonal therapy and dietary management.

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Hypotensive Reaction Following the Use of Glucagon

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There are no reported instances of sensitivity to glucagon. Recently we observed a severe hypotensive reaction immediately following the intravenous administration of glucagon. With the increased interest in glucagon, it appears advisable to report this reaction.

Report of Cases

The patient is a 52-year-old divorced housewife with a history of good physical health. Five years prior to this admission, on two separate occasions separated by two or three months, she received six to eight subcoma doses of insulin during psychiatric treatment at another location. Routine physical, neurological, and laboratory examinations at the time of admission to the Henry Phipps Psychiatric Clinic were within normal limits. Her diagnosis during this hospitalization was paranoid personality reaction.

The glucagon * was administered as a part of a study of the response to glucagon in a large group of persons. While the patient was in a fasting state and supine, a blood specimen was withdrawn from an anticubital vein. Five minutes later 4.7 cc. of glucagon solution was injected rapidly in an anticubital vein. Within 45 seconds the patient began to show evidence of massive circulatory collapse, as manifested by a marked drop in blood pressure; imperceptable pulse; vomiting; "needles" in her hands and feet; cool, palid, and moist skin, but no loss of consciousness. After 15 minutes 0.5 cc. of 1:1000 aqueous epinephrine solution was given intramuscularly. The patient responded slowly, returning to a normal state in several hours. The subsequent course was uneventful.

Skin tests were performed 20 days following this reaction. They consisted of intradermal injections of approximately 0.1 cc. each of distilled water, insulin diluting fluid,† μ100 units regular commercial insulin, and glucagon solution in the volar surface of the forearms. After 30 minutes, there were no demonstrable reactions at the site where the distilled water and the insulin diluting fluid had been injected. A raised erythematous area 1 cm. in diameter was present at the site of the insulin injection. A raised pale edematous area 1.5 cm. in diameter, surrounded by an irregular erythematous area measuring 2.6 cm. in diameter, was present at the glucagon injection site.

Comment

It seems clear that this patient suffered from a major hypotensive reaction directly attributable to the intravenous injection of glucagon. Material from the same vial had been used on previous occasions without untoward reactions, making the likelihood of contamination remote. Since commercial preparations of insulin are contaminated with small quantities of glucagon and the available preparations of glucagon are contaminated with small quantities of insulin, the previous administration of insulin to this patient may have initiated the development of sensitivity to these substances.

Both insulin and glucagon are of animal origin, proteins, and similar in chemical composition.[1] Sensitivity reactions to glucagon are therefore not unexpected. In this case the reaction could have been due to either insulin or glucagon. The results of skin tests appear to indicate that glucagon is the offender. The smaller reaction to the insulin solution could well be due to the amount of glucagon present in the insulin. The absence of previous reports of sensitivity to glucagon is probably due to the limited number of persons who have received the drug. It is therefore recom-

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From the Department of Psychiatry of The Johns Hopkins Hospital.

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* The glucagon employed in these studies was supplied by Dr. W. R. Kirtley, of Eli Lilly & Company.

† Insulin diluting fluid is the diluent for both insulin and glucagon.

mended that, in using glucagon, one must be prepared to deal with a reaction of this sort.

Summary

A case is presented in which a severe hypotensive episode followed the intravenous administration of a solution of glucagon. Skin testing appeared to indicate a sensitivity to glucagon.

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Eosinophilic Leukemia

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Eosinophilic leukemia is considered to be an extremely rare disorder. Wintrobe,[1] in the last edition of his text, points out that approximately 25 cases have been reported in which there was marked unexplained leukocytosis with striking eosinophilia. In the reported cases the relatively acute course was in sharp contrast to the consistent maturity of the eosinophiles in the peripheral circulation. The duration of illness in 14 of the patients was from a few days to 14 months. Enlargement of the spleen, liver, and lymph glands was not always present, but there was anemia and thrombocytopenia, and the leukocyte count ranged from normal to 265,000 per cubic millimeter. Death occurred in all the cases, and the findings resembled those of leukemia except for infiltration by eosinophilic cells instead of other forms. In several patients the terminal morphological picture was that of acute myeloblastic leukemia. Wintrobe further states that it seems justified to consider these cases as acute leukemia of an eosinophilic type. Gray,[2] in a review, found at necropsy a widespread infiltration of voluntary muscles, myocardium, pulmonary alveolar walls, white pulp, lymph glands, liver, and kidneys by mature eosinophiles. The cause of death in most patients was heart failure due to myocardial leukemic infiltrates. An interesting finding in 4 of the 23 reviewed cases was the presence of a cardiac mural thrombus. Other reports have not described this, however.[3-5]

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The following, we believe, represents a case of eosinophilic leukemia. The autopsy findings are described with emphasis on the interesting cardiac lesion which was present.

Report of Case

This 27-year-old American Indian man while on duty in Korea was first hospitalized Dec. 29, 1953, because of delusions of some three month's duration. He also complained of moderate cough for the past year. The physical examination at this time was not remarkable. His admission laboratory blood cell count revealed 3,760,000 red blood cells, with 11.6 gm. hemoglobin; hematocrit, 32%; WBC, 38,700, with 11% neutrophils, 14% lymphocytes, and 75% eosinophils. The remainder of the laboratory work, including serum proteins; stools for blood and parasites; sputum examinations for tubercle bacilli; trichinelli skin test; deltoid and gastrocnemius muscle biopsy; x-rays of soft tissues, and lungs and bone survey, were all within normal limits. His mental status rapidly improved, and he appeared to have recovered from his psychotic episode, which had been diagnosed as a schizophrenic reaction of the paranoid type. He was returned for a trial of duty and was to be checked again in a few weeks.

The patient returned to the ZI soon after and while at Camp Stoneman, Calif., was hospitalized May 27, 1954. The patient stated that he felt perfectly well until the day prior to admission, when he noted a slight dizziness. This was followed by epigastric discomfort and an episode of nonbloody vomiting. The dizziness persisted for about one day and then subsided. There had been no previous similar episodes. The general systemic review was noncontributory. Specifically, there was no dyspnea, loss of appetite or weight, bowel dysfunction, or gastrointestinal bleeding.

The patient did manual labor while in the Army, smoked one-half pack of cigarettes a day, and used alcohol occasionally. He had not been taking any medication prior to this illness and gave no history of drug sensitivity. The history was negative for malaria, hay fever, asthma, urticaria, and ingestion of uncooked pork.

The admission physical examination disclosed a well-developed, well-nourished 27-year-old man

who appeared neither acutely or chronically ill. The general physical examination was within normal limits, with the exception of a palpable spleen, the edge of which was felt 2 fingerbreadths below the costal margin. No abnormal masses were palpated. No lymphadenopathy was noted. The blood pressure was 114/80.

Repeated urinalyses were within normal limits, with the exception of the last week of hospitalization, when the urine contained 1 to 2+ albumin and 1 to 3+ sugar. The microscopic findings of the urine were always normal. Several blood cultures were sterile. Repeated stool examinations were negative for blood, ova, and parasites, with the exception of one specimen which contained Endamoeba nana. Six gastric washings were negative on smear and culture for acid-fast bacilli. The serologic test for syphilis was negative. The tuberculin test was positive 1+ in the first strength. The coccidiodin skin test was negative. Cerebrospinal fluid examination was normal. Hemoglobin, 11 gm. per 100 cc.; hematocrit, 36; WBC, 38,700, with 75% eosinophils, 11% neutrophils, and 14% lymphocytes; platelets, 160,000; bleeding time, 3 minutes; coagulation time, 10 minutes; B. U. N., 46; bilirubin, 0.4 mg. per 100 cc. direct and 0.6 mg. per 100 cc. total. The prothrombin time was normal, and the clot retraction was complete in two hours. The initial chest x-ray taken on the day of admission to the hospital revealed a circumscribed area of increased density measuring about 2.5×2.0 cm. in the left upper lateral lung field. The film of the abdomen revealed an enlarged spleen.

For complete hematology data see the Chart.

The patient's hospital course was characterized by a low-grade fever, the temperature occasionally reaching 101 F but usually not extending over 100 F. Shortly after admission, the patient developed pain in the left upper quadrant which increased rather considerably over a period of three or four days and then subsided. It was felt that this symptom might represent splenic infarction or perisplenitis. On June 5 the patient suddenly became confused and vomited. On the following morning he appeared lethargic and weak, and questionable petechiae appeared on the back and neck. On June 7 the patient given corticotropin (ACTH) intravenously and intramuscularly. Following the use of this drug, the patient's general clinical condition improved rather strikingly for a few days. He offered few complaints, ate well, and seemed cheerful. The low-grade fever persisted. A chest x-ray taken with a portable unit

HEMATOLOGICAL DATA

DATE	W.B.C. PER CMM	POLYS. %	EOSIN %	LYMPH %	MON. %	BASO %	R.B.C. MILLIONS PER CMM	Hb. GMS/100ML	Hct. %	PLAT. PER CMM	REMARKS
DEC. 30, '53	43,000	10	76	14			3.76	11.6	32		
JAN. 7, '54	30,000	5	80	15			4.82	14.3	47		
FEB. 5	27,500	12	71	16		1	4.92	14.7	48	190,000	TOTAL EOSINOPHIL COUNT 20,000 CU/MM
MAR. 12	25,400	21	67	12			4.76	14.3	48		
MAY 26	24,600	10	76	13		1		13.8	41		
JUNE 4										150,000	
5	45,500	16	75	9							ACTH. STARTED
7	39,400	21	71	8			4.06	11.0	36	160,000	BLEEDING TIME 3 MIN. COAG. TIME 15 MIN.
8	54,400	24	70	6							3% NUCLEATED RBC/100 WBC
10	29,600	51	38	11							
14	35,800	49	45	8				10.7	32		
15	32,100	43	55	2							ACTH. & TERMINATED
16	64,800	11	86	3							
17	42,600	18	79	3							
18	46,800	10	87	3							
22	58,000	28	62	10				9.5	32		
JUNE 24	30,200	33	55	12							

BONE MARROW STUDIES

	JAN. 4, 1954 %	JUNE 7 1954 %
MYELOBLAST	0	0
PROMYELOCYTE		
EOSIN	0	0
MYELOCYTE		
NEUT.	1	1
EOSIN	5	5
BASO.	0	0
METAMYELOCYTE		
NEUT.	1	8
EOSIN	12	7
BASO.	0	0

	JAN. 4, 1954 %	JUNE 7, 1954 %
P.M.N.		
NEUT. N.F.	4	4
NEUT. FIL.	8	15
EOSIN	35	40
BASO.	0	0
LYMPHOCYTE	15	13
MONOCYTE	0	0
PLASMACYTE	0	0
ERYTHROBLAST	0	1
NORMOBLAST	16	10
UNDIFF.	0	0

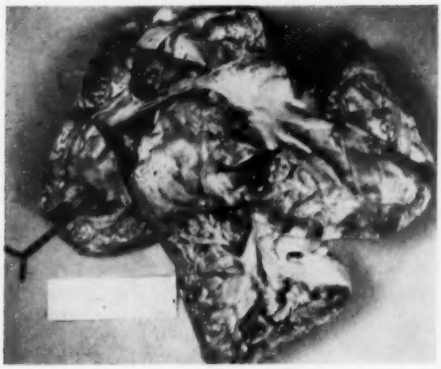

Fig. 1.—Gross photograph of heart. Mural thrombus (arrow) filling left ventricle.

on June 7 revealed a pneumonic process in the right upper and lower lobe. During the ensuing few days the pneumonic process increased, the possibility of a spreading pulmonary tuberculosis was entertained, and the corticotropin therapy was terminated. During the night of June 23 the patient's cough increased markedly and several episodes of vomiting occurred. The following morning he appeared much weaker, and tachycardia and gallop rhythm was noted. Respirations became progressively more shallow and rapid. The patient was rapidly digitalized and placed in an oxygen tent. His condition rapidly deteriorated, and he died at 2:20 p. m.

Portmortem Examination.—The external examination of the body revealed no abnormalities. When the chest was opened approximately 2000 cc. of yellowish serous fluid was noted in each thoracic cavity. At the apex of the right lung, fibrous adhesions were present between the visceral and parietal pleura. Numerous enlarged lymph nodes were noted in the mesentery, about the porta hepatis, and in the retroperitoneum. The largest of these lymph nodes measured approximately 2×2 cm. Similar nodes were noted in the mediastinum. Recent hemorrhage was evident in the retroperitoneal tissues.

Heart: Weight, 475 gm. Dissection of the larger coronary vessels revealed patency throughout. No thrombi or emboli were evident within their lumina. Dissection into the myocardium revealed at the apex and within the interventricular septum a hemorrhagic area which was soft and poorly demarcated. The posterior basal portions of both ventricles had a similar appearance. The cavity of the left ventricle was occupied by a soft thrombus which merged with necrotic ventricular muscle (Fig. 1).

Microscopic sections through the anterior apical portion of the left ventricle revealed the presence of a large mural thrombus. The endocardium at this point was destroyed, and there was an ingrowth of well-vascularized immature fibrous tissue representing granulations. Within the myocardium were present large areas having loss of cellular detail. At the margins of these areas there was proliferation of connective tissue which was densely infiltrated with mature eosinophils. The midventricular portion of the right ventricle revealed similar areas of necrosis, cellular infiltration, and hyperemia, as described in the left ventricle. The endocardium also had an attached

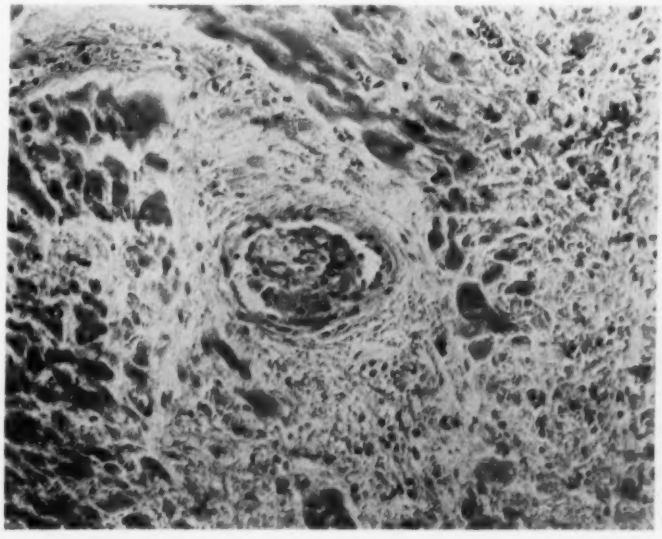

Fig. 2.—Photomicrograph of small coronary artery with luminal thrombus. The adjacent myocardial fibers have largely been replaced by fibrous connective tissue; reduced 1/9 from mag. ×150.

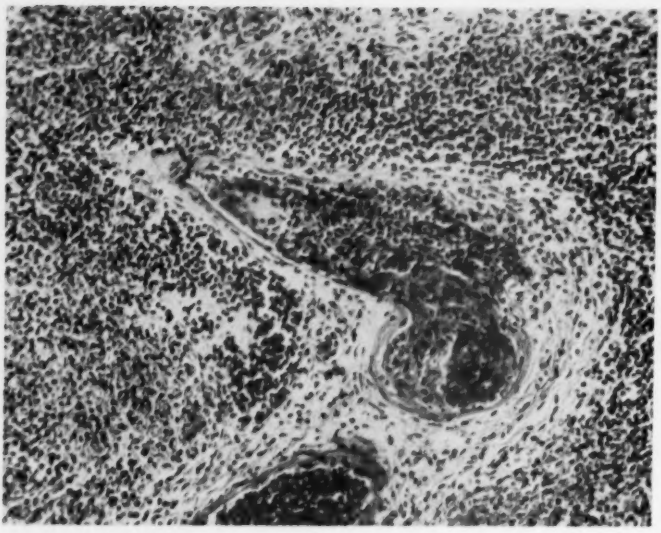

Fig. 3. — Photomicrograph of spleen. The large vessel is occluded by a thrombus with a peripheral infiltration of eosinophiles; reduced 1/9 from mag. × 150.

mural thrombus with early organization. The larger coronary vessels revealed no evident atherosclerotic process or thrombosis. However, many of the smaller coronary vessels were occluded by antemortem, laminated thrombi (Fig. 2). Angiitis was not evident.

Spleen: Weight 465 gm. The spleen revealed yellowish-tan areas of firmness extending throughout. The base of these lesions appeared to be on the capsule, with a roughly triangular area extending into the splenic pulp. The pulp elsewhere was coarsely granular and reddish-gray. Distinction between red and white pulp could not be made.

Microscopic sections of the firm yellowish areas revealed infarction. Medium-sized and small arteries were seen to be occluded by antemortem, laminated thrombi. The red pulp had numerous mature eosinophils, admixed with normal splenocytes. Angiitis was not evident. (Fig. 3).

Lymph Nodes: Sections of the mesenteric and mediastinal lymph nodes showed widely dilated sinusoids. These contained numerous eosinophils. The follicles were loose and infiltrated by eosinophils. A section of one mediastinal lymph node showed a large area of caseation necrosis with surrounding dense fibrous connective tissue. Special stains for acid-fast bacilli and fungi showed no organisms. Cultures failed to grow out organisms.

Bone Marrow: Abundant soft, gray-red marrow was evident, and microscopic sections showed a marked cellular appearance. The predominant cell was the eosinophil, with conspicuous eosinophilic, cytoplasmic granules. In addition, many immature eosinophils could be identified. There was a moderate number of megakaryocytes. Erythrocytic and neutrophilic precursors were greatly reduced in number.

Microscopic study of the remaining viscera showed a moderate infiltration with similar mature eosinophilic leukocytes. Grossly there was hemorrhage into the renal pelves. No gastrointestinal or muscular parasites were found, and no other significant gross or microscopic abnormalities were present.

Comment

This case is considered to be one of acute eosinophilic leukemia. No known etiologic factors that may give rise to eosinophilia were discovered before death or at autopsy. Tissue infiltrates by mature eosinophils were present. Within the bone marrow many immature eosinophils could be identified. In peripheral blood smears the numerous mature esoinophils had coarse eosinophilic cytoplasmic granules and vacuoles. According to Custer,[6] this latter finding is helpful in distinguishing eosinophilic leukemia from an eosinophilic leukemoid reaction. The myocardial infiltration has been observed frequently, and infarctions have been considered quite typical of eosinophilic leukemia. We believe that vascular thrombosis led to the myocardial infarction and the subsequent formation of the mural thrombus.

In a recent review Engfeldt and Zetterström [7] propose an allergic etiology for cases which have been reported as eosinophilic leukemia. They believe a more appropriate designation would be disseminated eosinophilic collagen disease. In our case insufficient evidence is offered for this assumption. The only suggestion of any relationship was the presence of small vascular thrombi. However, these seemed clearly unrelated to the presence of an angiitis such as is found in the generally accepted group of collagen diseases. Their statement that the histological findings in the myocardium, with scar tissue showing only slight infiltration of inflammatory cells alternating with more acute lesions with edema and disintegration of muscle fibers, can hardly be interpreted as being dependent upon leukemic infiltration is a reasonable one. However, these areas are interpreted by us to represent foci of infarction. It must be admitted that the presence of the small-vessel thrombi in the absence of vascular lesions is difficult to explain. These are not infrequently observed in other forms of leukemia and may be related to endothelial injury, perhaps anoxia.

Summary

The clinical and pathological findings in a case of fatal leukemia are presented.

The clinical course was acute, with the proliferating cell being the eosinophil. Postmortem studies of the tissues revealed infiltration of many organs by mature eosinophils. A striking finding was a left ventricular myocardial infarction with an associated left ventricular mural thrombus.

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Micrococcus Tetragenus Septicemia

Report of a Case Including Subacute Bacterial Endocarditis of the Pulmonic Valve and Mycotic Aneurysm, with Autopsy Findings and Review of the Literature

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The organism Micrococcus tetragenus (Gaffkya tetragena)[1] is a small encapsulated Gram-positive coccus occurring in clusters of four which was discovered by Koch and Gaffky,[2] in 1881. It was first thought to be nonpathogenic, but was described by Jakowsky, in 1886, cited by von Ofenheim,[4] to cause septicemia. The first reports in the American literature were by Griewe, in 1899, and by Steele, in 1914, both cited by Reimann.[5] The subject was reviewed from a clinical and bacteriological viewpoint by Reimann,[5-9] in 1935-1937. At this time he reported only 170 cases of infection due to M. tetragenus in the entire literature, and many of these were incomplete case reports. In another review of the subject by Boynton,[10] in 1950, there were only 10 authenticated cases of subacute bacterial endocarditis due to M. tetragenus, and Boynton's case (which included septicemia and meningitis), which was reported in some detail with autopsy findings, was the second authenticated case in American literature.

Another excellent review, by Leach and Medinger,[11] states that all the reports are about single cases except for two mild epidemics which occurred during World War I (Steele, cited by Reimann[5]). According to Reimann[5-9] and to Leach and Medinger[11] the organism is generally of low virulence and becomes pathogenic only under certain conditions where the resistance of the host is lowered. When infection does occur due to M. tetragenus, it resembles septicemia with metastatic localization, somewhat similar to staphylococcal infections, with the difference that it has a greater predilection for serous surfaces, including the meninges, the joints, and the peritoneal cavity. In his review of this subject before the advent of antibiotics (i. e., in 1935-1937) Reimann[5-9] states that there was a mortality rate of 50% in 44 cases of M. tetragenus septicemia where the outcome was stated.

This infection is commonest in young adults but may occur in any age group. Males predominate over females 3:1. Reimann[5-9] states that it is usually preceded by some factor which lowers the resistance of the host, such as sore throat or respiratory infection. M. tetragenus is a normal "flora" in the nasopharynx, and that is believed to be the usual portal of entry. It has been seen to follow or coexist with typhoid fever or brucellosis. The course of infection may be mild or severe; the patient may die in 7 days, or there may be a protracted course lasting 7 to 12 months.

In cases of septicemia, the onset is usually abrupt, characterized by chills and spikes of fever to 105 or 106 degrees F, malaise, and generalized aching. Patients usually complain of bachache or bone aches. There is usually a mild to moderate leukocytosis and splenomegaly. Other symptoms depend

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on the site of metastatic localization, as in the case of localization in the meninges, arthritis, respiratory lesions (multiple lung abscesses), mouth infections, pneumonia, empyema, peritonitis, perinephric abscess, pyosalpinx, and renal infection. Pinck and Zheutlin [12] have even described a penile ulcer due to M. tetragenus.

The diagnosis depends on the isolation of the organisms from blood cultures in septicemia or from other sites or organs in cases of metastatic involvement. This is not always easy to accomplish in these days of widespread massive doses of broad-spectrum antibiotics.

The following case is of interest for several reasons. For one thing, the pattern of illness was characteristic of septicemia; but the organism was not identified until after the antibiotics were stopped, and blood cultures were taken while the patient was off antibiotics. This did not happen until the patient had been in the hospital for two weeks, and the antibiotics did not seem to be helping him. It was then decided to stop administration of antibiotics and establish the diagnosis bacteriologically. He was later successfully treated with massive doses of penicillin (up to 55,000,000 units a day). Penicillin was the only antibiotic to which the micro-organism was sensitive in this case.[15] Another point of interest is the apparent involvement in succession of skin, eyegrounds, liver, heart, meninges, lungs, joints, gallbladder, and, probably, kidneys. The organism was identified in blood cultures, however. Cultures of spinal fluid, joint fluid, and urine and from the gallbladder (at cholecystectomy five months later) were sterile or grew other micro-organisms.

It is also of considerable interest and speculation that the heart was apparently normal at the time of the first admission, that the endocarditis involved the pulmonic valve, which is by far the rarest valve to be involved in any type of endocarditis, and that there was probably neither rheumatic nor congenital heart disease as a forerunner for this rare endocarditis.

In one study by M. Zanchi and L. Stival [13] of 911 autopsied cases of all types of bacterial endocarditis (at the University of Milan, Italy, in 1952), there were only 2 cases (out of the total of 911) where the lesion involved the pulmonic valve. Unfortunately these cases are not discussed in detail by the authors. There was also one case where all four valves were involved (mitral, aortic, tricuspid, pulmonic) in this series of 911 autopsied cases.

There have been a few isolated case reports of endocarditis of the pulmonic valve; but this is more common in acute bacterial endocarditis (caused by gonococcus or pneumococcus)[16,17] than in subacute bacterial endocarditis due to a viridans Streptococcus. In their recent book on "Differential Diagnosis,"[16] Harvey and Bordley cite a case from the Clinical-Pathological Conference at the Johns Hopkins Hospital in 1933 in which Dr. Louis Hamman correctly diagnosed the site of the lesion in a case of a viridans Streptococcus subacute bacterial endocarditis on the pulmonic valve. This turned out to be the case at autopsy, though during the patient's life time the clinicians had assumed that the patient had aortic insufficiency and subacute bacterial endocarditis of the aortic valve. Dr. Hamman made the correct diagnosis that the pulmonic valve was involved by the absence of peripheral signs of aortic insufficiency (such as Corrigan's pulse and left ventricular hypertrophy and failure) and the presence of pulmonary infarcts. Such case reports are isolated and are few and far between. This present case is the first case of M. tetragenus endocarditis of the pulmonic valve to be reported.

Lastly, it is of interest that this patient ran an extremely prolonged course and was possibly or probably "cured" (bacteriologically) of his septicemia due to M. tetragenus, only to return three years later to die of lobar pneumonia due to pneumococcus

Type III (from blood culture and sputum), and no evidence of a M. tetragenus infection or septicemia was found at this time. At the time of autopsy the pulmonic valve was extensively destroyed. Unfortunately, the patient was lost sight of in the two and one-half years between his two hospital admissions.

Report of Case

A 64-year-old Polish male cook was admitted to First (Columbia University) Surgical Division of Bellevue Hospital on May 16, 1951, complaining of fever, anorexia, abdominal pain, obstipation, and jaundice of five days' duration. He had been entirely well before the onset of his illness, which was acute. He was transferred to the First Medical Division two days later and remained in the hospital for 8 months (34 weeks) on this first admission. On admission he was acutely ill, with temperature to 104 degrees F; P., 140; R. 38, and B. P., 150/105. At the time of admission, his skin was slightly icteric. There was cellulitis, with an eczematous eruption over both forearms and the dorsum of both hands. There were scattered wheezes and rhonchi at both lung bases, with rales at the right base posteriorly. There was a regular tachycardia which ranged between 120 to 140 for the first week of his hospital stay, and no heart murmurs were noted at this time. A systolic murmur over the entire precordium, loudest at the pulmonic area, was first noted in the second hospital week and became progressively louder for the next three weeks. A diastolic murmur in the third anterior interspace to the left of the sternum (the pulmonic area) was first noted on June 6, 1951, three weeks after admission.

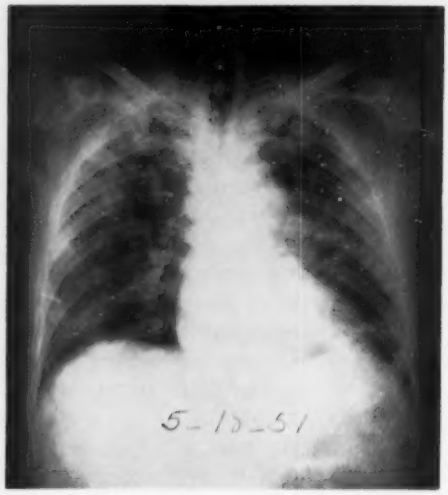


Fig. 1.—Chest x-ray, second hospital day.

The patient was so acutely ill on admission that he was given penicillin, 2,400,000 units; streptomycin, 1.0 gm.; chloramphenicol (Chloromycetin), 1.5 grains (0.1 gm.), and chlortetracycline (Aureomycin), 2.0 grains (0.13 gm.) a day before blood cultures were taken. The doses of chloramphenicol and chlortetracycline were cut on the second day, and he was maintained for 15 days on penicillin, 2,400,000 units, and streptomycin, 1.0 gm., a day. During this period the laboratory data (Tables 1 and 2) were as follows: On admission Hgb. was 12.5 gm. per 100 cc., but by the end of the first week it had fallen to 10 gm. with 3,290,000 RBC.

TABLE 1.—*Laboratory Data*

Date	Blood Culture	Hgb., Gm./ 100 Cc.	RBC, Million/ Cu. Mm.	WBC, Thousand Cu. Mm.	P.M.N., per Cent	Other
5/22/51	Neg.	12.5		5.0	80	NPN, 129 mg./100 cc.
5/23/51	Neg.	10	3.3	12.0	82	ESR, 45 mm./hr.
6/ 1/51	Neg.	7.5		6.1	78	BUN, 63 mg./100 cc.
6/ 2/51	Pos. for M. tetragenus 2×					
6/ 4/51	Neg.	8.0		5.4	75	BUN, 29 mg./100 cc.
6/ 5/51	Pos. for M. tetragenus 2×					Ceph. flocc., 3+ Alk. phos., 5 units
6/ 6/51	Pos. for M. tetragenus					
6/ 8/51	Pos. for M. tetragenus					
6/11/51	Neg.	11		9.5	74	Ceph. flocc., 2+
6/12/51	Neg.					
6/13/51	Pos. for M. tetragenus					
6/14/51	Pos. for M. tetragenus	10.5	3.06	14.5	86	
7/ 4/51	Neg.			6.9	50	Blood sugar, 107.5 BUN, 15 mg./100 cc.
8/23/51	Pos. for M. tetragenus	13.5		8.9	74	
9/14/51	Pos. for M. tetragenus	12		12.3	62	
12/ 5/51	Pos. for M. tetragenus			7.1	68	

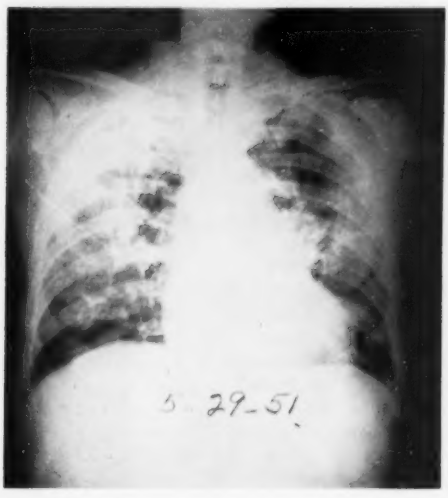
TABLE 2.—*Sensitivity Studies and Additional Laboratory Data*

	Sensitivity Studies on M. Tetragenus for Blood Culture		
6/8/51	Penicillin	3.1 γ/cc.	Sensitive
	Oxytetracycline (Terramycin)	50 γ/cc.	Resistant
	Chlortetracycline	50 γ/cc.	
	Chloramphenicol	Totally resistant	
	Streptomycin	Totally resistant	
	Urinalysis		
5/16/51	Sp. gr., 1.013 Albumin, 3+ Sugar, neg. Acetone, neg. Bile, pos. Microscopic findings, loaded with WBC		
6/ 1/51	Sp. gr., 1.006 Albumin, 1+ Sugar, neg. Microscopic findings, 6-8 WBC/high-power field		

WBC was 5000 on admission, with 80% P. M. N. forms; on the third day it was 12,100, with 82% P. M. N. forms, and thereafter it varied between 5000 and 10,000. Urine showed a specific gravity of 1.013, with 3+ albumin and no sugar and was loaded with WBC; later it also showed RBC. It was 1+ positive for bile and 2+ positive for urobilinogen. The NPN was 129 mg. per 100 cc. on admission, and by the end of the 1st week the BUN was still elevated at 63 mg. per 100 cc. His jaundice, which was slight on admission, deepened during the first week. The icterus index was 60 units; total protein, 4.8 gm. per 100 cc.; albumin/globulin ratio 3.7/1.1; serum bicarbonate, 36 mEq. per liter, and chlorides, 99 mEq. per liter (Table 1.)

On June 1 his condition was somewhat improved, and antibiotic therapy was stopped. During the next two weeks, 22 blood cultures were drawn while the patient was not given antibiotic therapy. Of these 22 cultures, 9 were positive for M. tetragenus (8 of the 9 in two bottles, the 9th in one bottle only). Urine culture during this time grew a Proteus organism, and one bottle of one blood culture bottle showed Staphylococcus aureus in addition to M. tetragenus.

Fig. 2.—Chest x-ray, 14th hospital day.



During the first week, while he was still given antibiotic therapy, he developed a severe progressive jaundice and maculopapular skin lesions over chest and abdomen (lesions were 5 mm. in diameter); rales in both lungs increased; he developed a systolic murmur over the precordium loudest over the pulmonic area; the liver and spleen became palpable, and he also developed a Roth spot in the right fundus.

During this time he also developed signs of meningitis, including nuchal rigidity and a positive Kernig sign. A lumbar puncture was performed on May 22, 1951, which revealed slightly xanthochromic fluid (patient was jaundiced at the time), with an initial pressure of 95 mm. of water and a final pressure of 40 mm. of water. The fluid was clear and showed 1+ Pandy; protein, 50 mg. per 100 cc.; sugar, 172 mg. per 100 cc. (post infusion), and chlorides, 117 mEq/liter and contained 10 WBC (all lymphocytes) and 40 RBC per high-power field. The spinal fluid was sterile on culture, as it was during the time that the patient was still given antibiotic therapy.

During the second hospital week, though still very ill, he was somewhat improved. It was during this time, June 1 to 14, that antibiotic therapy was stopped and that the positive blood cultures for M. tetragenus were obtained. The patient's temperature ranged between 100 and 102 degrees F. On June 4, the right knee was swollen, hot, and tender. A small amount of fluid was withdrawn which was sterile on culture. The diastolic murmur at the left sternal border was first heard on June 6, 1951, while the patient was not receiving antibiotics. It continued to be easily audible throughout his hospital stay.

When the organism (M. tetragenus) was isolated repeatedly from blood cultures and when it was found to be more sensitive to penicillin than to other antibiotics (Table 2), he was treated with massive doses of penicillin. Beginning on June 14, 1951, (his fourth hospital week) he received 2,000,000 units of penicillin a day, which was increased stepwise until Aug. 4 to 13, when he received 40,000,000 units of penicillin daily by intravenous drip. His temperature, which had ranged between 100 and 102 degrees F when antibiotics were withdrawn, fell to the 99 to 100 degrees F range, and he felt well and looked much improved. There was no further evidence of septicemia or septic emboli. The BUN and liver chemistries became and remained normal during this period, and weekly urinalyses showed only 1+ albuminuria and negative sediment. The diastolic murmur which was first noted on June 6, 1951, during this time became progressively louder and was heard over the entire precordium but was the loudest in the third left intercostal space. The harsh systolic murmur remained unchanged. His blood pressure continued at 160/110, and the spleen tip remained palpable. Intravenous pyelograms were normal. Sputa and gastric cultures were negative for acid-fast bacilli, as was a tuberculin skin test (PPD No. 1 and No. 2). Although glucose tolerance and fasting blood sugar were elevated in June, he never had glycosuria, and his fasting blood sugar returned to normal in July and remained normal thereafter.

On Aug. 14, 1951, penicillin was stopped, and during August and September he did not receive any antibiotic therapy whatsoever. During this time he ran a low-grade fever (temperature to 103 degrees F), and of numerous blood cultures, only two were positive for M. tetragenus on Aug. 23 and Sept. 14, 1951. His other signs remained unchanged, and he was clinically well and up and about on the ward. On Oct. 2, 1951 he developed crampy upper right quadrant pain, tenderness over the gallbladder area, jaundice, and fever (temperature to 101 degrees F). Cholecystogram showed nonfilling of his gallbladder. Diagnosis was made of acute cholecystitis and probably cholelithiasis. He was treated symptomatically, and antibiotic therapy was resumed with 2,000,000 units of penicillin a day and 1.0 gm. of streptomycin a day. The symptoms subsided in a week but recurred in the early part of November. On Nov. 14, 1951, he had a cholecystectomy, at which time a markedly thickened and adherent gallbladder containing many small stones was removed. The common duct was free from stones by exploration and cholangiogram. Other abdominal viscera, including liver and spleen, appeared and felt normal at the time of surgery. Gallbladder cultures grew hemolytic enterococci but no M. tetragenus. He had an uneventful postoperative course and received chlortetracycline, 2.0 gm. once a day, and sulfadiazine, 2.0 gm. once a day, for two weeks. He became afebrile and asymptomatic and was discharged on Dec. 31, 1951, four weeks postoperatively. A routine blood culture was taken on Dec. 5, 1951, and was positive for M. tetragenus.

Unfortunately the patient never returned to clinic as he had been instructed to do. He was next seen two years and three months later very acutely ill. His second admission was March 17 to 19, 1954. He entered the emergency ward with the complaint of progressive weakness and cough for two weeks before admission. The patient was prostrated, acutely ill, and confused at the time

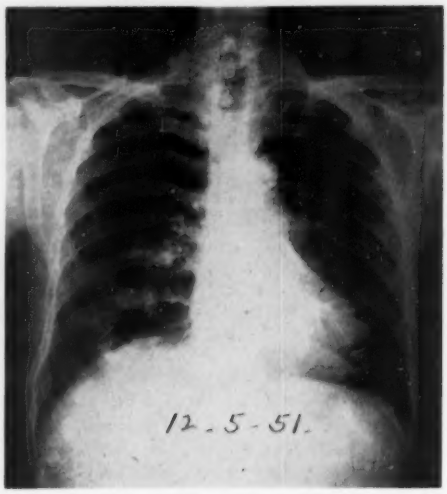
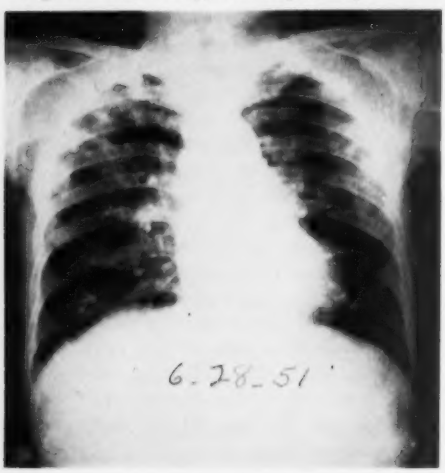


Fig. 4.—Chest x-ray at time of discharge after first hospital admission.

Fig. 3.—Chest x-ray, 43d hospital day.



of admission, so that an interval history was not obtainable. The cough became much worse and became productive of blood-streaked sputum two days before admission.

Physical examination showed a cyanotic confused acutely and chronically ill white man with dyspnea and tachypnea. Temperature was 104 degrees F; pulse, 120 (regular); respirations, 34, and blood pressure, 120/75. There was slight icterus of the sclerae, and one Roth spot was seen in the left fundus. His neck was supple. There was no lymphadenopathy. There were coarse rhonchi throughout both lung fields and signs of lobar consolidation over the lower two-thirds of the left chest posteriorly. The heart was not enlarged by percussion; the sounds were of good quality, with a regular sinus tachycardia at 120 to 130 per minute. There was a harsh systolic murmur as before and a diastolic murmur loudest in the third left interspace transmitted down the left sternal border. No gallop or rub was heard. The liver was down 2 fingerbreadths below the right costal margin. The spleen was not felt. There was 2+ ankle edema. Findings on rectal and neurological examinations were negative.

Chest x-ray showed consolidation (lobar pneumonia) of the entire left lung field and a hilar density on the right (Fig. 5). Electrocardiogram showed sinus tachycardia and right axis deviation but was otherwise within normal limits and showed no change from previous tracings in 1951.

Laboratory Data.—Hemoglobin was 8.5 gm. per 100 cc. on admission and rose to 11.0 gm. after a transfusion of packed red blood cells. Hematocrit was 39%. WBC was 12,500, with 93% polymorphonuclears and 7% lymphocytes. Urine showed specific gravity of 1.003, 2+ albumin, and 1+ glucose, and the sediment showed granular casts, 2-4 WBC per high-power field, and 20 RBC per high-power field. BUN was 30 mg. per 100 cc. CO_2, 24.3 mEq. per liter; chlorides, 112 mEq. per liter; potassium, 5.3 mEq. per liter; sodium, 129 mEq. per liter. Icterus index was 12 units; total protein was 5.3 gm. per 100 cc., with albumin 3.4 and globulin 2.1.

The most important laboratory finding was a blood culture which grew Type III pneumococcus and a sputum culture in which type III pneumococcus was the predominant organism. The sputum culture also showed Staphylococcus aureus, coagulase-positive; Proteus organism, and a viridans Streptococcus. There were no M. tetragenus in blood or sputum cultures on this admission.

The patient was placed in an oxygen tent and was given heroic therapy: 30,000,000 units of penicillin in the first 24 hours intravenously, 1.0 gm. of streptomycin intramuscularly, and a transfusion of 500 cc. of packed red blood cells. He did not improve. On the second hospital day he went into shock and pulmonary edema which failed to respond to intravenous digoxin and meralluride (Mercuhydrin). An electrocardiogram on March 18, 1954, showed sinus tachycardia with a ventricular rate of 140 per minute and frequent ventricular and supraventricular extrasystoles. In addition to all the above mentioned therapy he was given intramuscular quinidine, which decreased the frequency of the extrasystoles but failed to relieve the fatal combination of shock, pulmonary edema, and overwhelming septicemia. He died on the third hospital day, March 19, 1954. An autopsy was performed six days later.

Autopsy Report (Dr. Marvin Kuschner, Pathologist, Bellevue Hospital).—The autopsy was performed six days after death. The main findings of interest both macroscopically and microscopically were in the heart and the lungs.

The heart weighed 370 gm. and was of unusual shape in that the right ventricle made up more than the usual portion of the apical part of the heart. The myocardium was of normal consistency and appearance, but the right ventricle was dilated and its wall, which measured 0.9 cm. in thickness, was strikingly hypertrophied. The right auricle was likewise hypertrophied and dilated. The left ventricle was normal in size, and its wall measured 1.3 cm. in thickness. The tricuspid and aortic valves were entirely normal. The mitral valve had a slightly elevated glistening plaque approximately 0.2 cm. in its greatest diameter along the free border of the valve on its atrial surface.

The pulmonic valve had only two recognizable cusps; what remained of the third cusp was an irregular nodular piece of tissue measuring 1×0.3

Fig. 5.—Chest x-ray on day of second hospital admission, two days before death from lobar pneumonia.

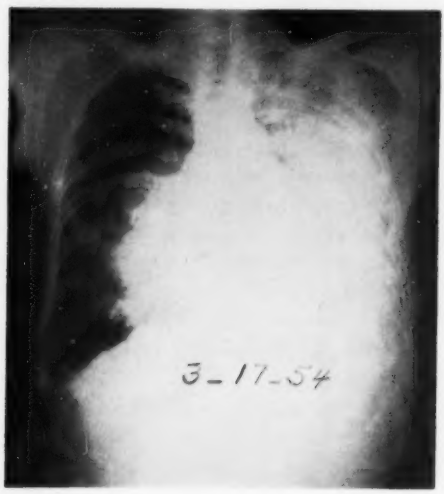


Fig. 6.—Pulmonic valve and saccular aneurysm at autopsy, March 25, 1954.

cm. and attached to its original base only at one end. The surface of this knob of tissue was glistening and endothelialized and the other two cusps were firm and thickened. There was thus a marked valvular insufficiency. In addition, there was a saccular aneurysm 2.4 cm. in its greatest diameter at the base of the pulmonary artery, with several smaller compartments within it (Fig. 6) The coronary arteries were patent and unremarkable except for one or two atheromatous plaques.

The left lung weighed 1400 gm. and the right lung weighed 1370 gm. The pleura over both lungs was thickened and was separated from the parietal surfaces with difficulty. There was no free fluid in either pleural cavity. The entire left lung was solid to palpation and inelastic, and the cut surface was airless, granular, and translucent throughout. It was not edematous.

The right lung contained scattered patches of the same type of granular translucent areas as characterized the entire left lung. In addition, however, the right lung showed a moderate amount of edema, and the cut surface was deep red. The bronchi were diffusely reddened, and pinkish fluid oozed from them. The pulmonary vessels were unremarkable and contained no thrombi.

Microscopic Examination.

Heart: Left Ventricle. The muscle fibers were of normal size. There was some increase in dispersed interstitial mononuclear cells. Coronary arteries showed moderate medial hypertrophy.

Right Ventricle. There was moderate hypertrophy of the fibers and some increase in scattered interstitial mononuclear cells.

Pulmonic Valve. Section through the destroyed cusp revealed that it was made up of dense acellular hyaline connective tissue heavily infiltrated by mononuclear cells and lymphocytes. The remnant of the cusp was covered by endothelium. No bacteria were seen on special stains. The elastic tissue of the ring was interrupted, fragmented, and reduplicated.

"Mycotic" Aneurysm. Sections through the aneurysmal sac showed that it was made up of fibroelastic tissue, with no smooth muscle. There was no inflammatory reaction, and the endothelium was intact.

Mitral Valve. There was calcification at the annulus. It was otherwise normal.

Lungs: Sections of the left lung revealed the alveoli to be filled with an exudate composed of fibrin and mononuclear cells undergoing organization. Some alveoli also contained moderate numbers of red blood cells. The pleura was thickened and adherent to the parietal pleura, and in this dense connective tissue there were many blood vessels, including large thick-walled arteries. The right lung revealed focal groups of alveoli filled with an exudate of polymorphonuclear leukocytes and fibrin and some alveoli with hemosiderin-laden macrophages. In other areas the alveoli contained edema fluid.

Other Organs: The liver contained small areas of focal necrosis and showed the changes of mild chronic congestion. The spleen was the site of reactive splenitis. The kidneys contained focal areas of scarring apparently due to old pyelonephritis. There were no recent areas of abscess for-

Fig. 7.—Pulmonic valve at autopsy.

mation, nor were there evidences of embolic phenomena secondary to bacterial endocarditis found.

Anatomical Diagnoses: 1. Bacterial endocarditis of pulmonic valve with complete rupture of the left anterior cusp of the pulmonic valve and mycotic aneurysm formation at the base of the pulmonary artery, healed due to M. tetragenus by history. 2. Hypertrophy of right ventricle and right auricle. 3. Lobar pneumonia, left lung, organizing due to Type III pneumococcus. 4. Lobular pneumonia, right lung. 5. Old healed pyelonephritis.

Comment

This represents a unique case of bacterial endocarditis caused by M. tetragenus (an unusual organism), with an unusual site of implantation on the pulmonic valve. The organism was implanted on a previously undamaged valve. No stigmata of rheumatic heart disease or other valvular lesions were found. There was no significant myocardial scarring.

The portal of entry of this organism is unknown, although evidence of an old renal infection suggests the kidneys as a possible portal of entry. Alternatively the portal of entry may have been the gallbladder. At the time of cholecystectomy, in November, 1951, the gallbladder was found to be the site of a severe chronic inflammatory reaction. The throat or respiratory tract may also have been a portal of entry.

Whatever the portal of entry, the patient responded well to his prolonged course of penicillin therapy in 1951. At the time of autopsy, in 1954, there was no morphologic evidence of recent active bacterial endocarditis or of metastatic abscess formation. The pulmonic valve was extensively damaged. The diastolic murmur in the third left interspace, which had been interpreted as evidence of aortic insufficiency during the patient's life time, was due to a very marked degree of pulmonic valve insufficiency. Several observers had noted that the patient never showed the peripheral evidences of aortic insufficiency, such as Corrigan pulse, and until this terminal episode there was no evidence of left ventricular failure. This was explained by the fact that the pulmonic valve was involved rather than the aortic valve, producing the syndrome of pulmonic insufficiency.[16] The hypertrophy of the right ventricle is also explained by the extensive degree of pulmonic valvular insufficiency. His death was due to extensive involvement of both lungs by Type III pneumococcal lobar pneumonia, which at autopsy showed all the classic pathological evidence of a typical lobar pneumonia. This was in no way related to his previous endocarditis, which can be considered to have "healed" under antibiotic therapy.

This case was of interest from several points of view: 1. Septicemia and endocarditis caused by M. tetragenus have already been discussed in detail. 2. The involvement of the pulmonic valve only is an extremely unusual occurrence, as the pulmonic is the rarest of all valves to be involved by bacterial endocarditis. The fact that the valve was previously undamaged is also of interest. 3. This case can be classified as a successfully treated case of endocarditis due to M. tetragenus from a bacteriologic viewpoint, although there was massive damage to the pulmonic valve, and pulmonic insufficiency was a contributory factor in the patient's death from pneumococcal lobar pneumonia.

Summary

A case is presented of septicemia and endocarditis due to Micrococcus tetragenus, with a review of the literature. This is the first recorded case of M. tetragenus endocarditis in which only the pulmonic valve was involved.

45 East End Ave. (28).

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CORRECTION

In the article "Primary Carcinoma of the Liver: A Clinicopathologic Study of One Hundred Eight Cases," by Dr. Richard A. MacDonald (February issue, pp. 266-279) a line of type was transposed in the first paragraph on page 272. The last two sentences of this paragraph should read as follows: "In three patients, however, with normal albumin-globulin ratios the formol gel tests were positive. There was no way to determine whether these results were due to the presence of an abnormal globulin fraction, although this appeared to be a possible explanation."

In Table 1 of the same article (p. 273) the first entry in the first column should read "Healed yellow atrophy" and the heading of the right-hand column should be "Per Cent with Carcinoma."

High Blood Pressure

Scientific Exhibits

A New Approach to Its Management

HAROLD B. EIBER, M.D., New York

This exhibit presents a graphic report on two studies, both of which were designed to evaluate chlorpromazine hydrochloride and Rauwolfia serpentina used in combination. The first study is an extensive investigation of the combination in the treatment of 350 hypertensive patients; the second, a preliminary trial of the combination in 50 neuropsychiatric patients.

Hypertensive Study

Unfortunately there is no safe, effective single drug for the treatment of moderate and severe hypertension. The potent drugs commonly used in these conditions (hexamethonium, pentolinium, the veratrums, hydralazine, et al.) are fairly unpredictable in action, and because the margin between their effective and toxic dose is small, the side-effects which they cause are numerous, annoying, and not infrequently dangerous.

Rauwolfia serpentina, an agent capable of producing a slow, gradual lowering of blood pressure, has been found valuable in treating mild hypertension. Chlorpromazine, which often exerts an immediate, slight hypotensive affect as a hypotensive agent, has also been reported capable of potentiating the action of several drugs, particularly opiates and sedatives. Consequently, it was felt that a synergistic action might result from combining chlorpromazine with Rauwolfia serpentina and that the combination might provide an effective treatment for moderate and severe hypertension.

To test this hypothesis, an 18-month study was conducted on 350 patients: 125 mild hypertensives; 125 moderate hypertensives; 100 severe hypertensives.

The study of chlorpromazine-Rauwolfia serpentina whole crude root combination in hypertensive patients clearly brought out the potentiating properties of chlorpromazine on Rauwolfia. This property enabled us to give a lower—and therefore safer—dose of both medications, with results more effective than higher doses of either chlorpromazine or Rauwolfia given alone. These studies have led us to initiate investigations of the potentiating effect of chlorpromazine on other hypotensive agents.

This study also indicates that the chlorpromazine-Rauwolfia combination may be more effective than either of its two components in treating various neuropsychiatric conditions.

Submitted for publication Dec. 9, 1956.

New York Medical College, Metropolitan Medical Center.

Shown as a Scientific Exhibit of the Section on Experimental Medicine and Therapeutics at the 104th Annual Meeting of the American Medical Association, Atlantic City, N. J., June 6-10, 1955.

CHLORPROMAZINE* PLUS RAUWOLFIA

In HYPERTENSION

Chlorpromazine: 1 markedly reduces the anxiety which frequently accompanies and sometimes causes hypertension.

2 potentiates the hypotensive action of rauwolfia.

Rauwolfia: 1 exerts a mild hypotensive effect.

2 is less depressing and produces fewer side-effects than any of its alkaloids used alone.

Combined the two drugs act synergistically to provide a safe, effective treatment for severe hypertension.

(Note: Studies in progress suggest that chlorpromazine may also be combined successfully with either hexamethonium, pentolinium, the hydralazines, or the veratrums.)

In NEUROPSYCHIATRIC CONDITIONS

The combination's success in treating hypertension prompted an investigation of its effect in treating 24 patients with either psychotic, psychoneurotic, or psychosomatic complaints.

11 of these patients had previously received either chlorpromazine, rauwolfia, or reserpine alone. 9 of them had better results with chlorpromazine combined with either rauwolfia or reserpine.

Of the 24 patients treated, 18 showed a marked, rapid improvement with the combination.

Dose: Mild cases - Chlorpromazine 25 mg.; rauwolfia 50mg., q.i.d.

Severe cases - Chlorpromazine up to 800 mg. daily; rauwolfia, no more than 300 mg. daily.

SIDE EFFECTS

Other investigators have reported that a small percentage of patients treated with chlorpromazine* develop an obstructive type of jaundice which disappears following withdrawal of the drug.

However, there were no instances of jaundice (or other serious side effects) observed in this study of over 350 patients.

* Thorazine, Smith, Kline & French Laboratories

Fig. 3.—Site of action of hexamethonium. Ganglionic blockade.

Fig. 4.—Site of action of pentolinium. Ganglionic blockade.

Fig. 5.—Site of action of the Veratrum compound. Central sympathetic inhibition; parasympathetic stimulation; afferent stimulation of vasomotor centers.

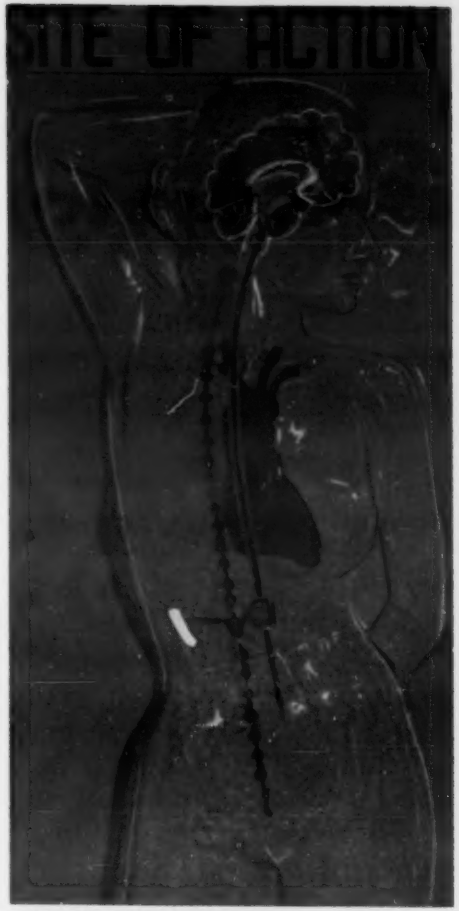


Fig. 6.—Site of action of hydralazine. Direct vasoldilator.

Fig. 7.—Site of action of Rauwolfia serpentina hypothalamus; central sympathetic inhibition; parasympathetic stimulation; cortical and subcortical levels in cerebrum; hypothalamus; medulla; peripheral autonomic nervous system.

Fig. 8.—Site of action of chlorpromazine. Parasympathetic stimulation; cortical and subcortical levels in cerebrum, hypothalamus, medulla; peripheral autonomic nervous system.

Fig. 9.—Site of action of the combination of chlorpromazine and Rauwolfia serpentina. A "chemical frontal lobe lobotomy" occurs with interruption of the corticothalamic tracts.

Fig. 10.—Side-effects of hexamethonium. Syncope; blurred vision; cerebral infarction; coronary insufficiency; circulatory collapse; paralytic ileus; diarrhea; urinary retention; impotence.

Fig. 11.—Side-effects of pentolinium. Syncope; blurred vision; paralytic ileus; impotence.

Fig. 12.—Side-effects of the Veratrum compounds. Syncope; coronary insufficiency; epigastric burning; vomiting; circulatory collapse.

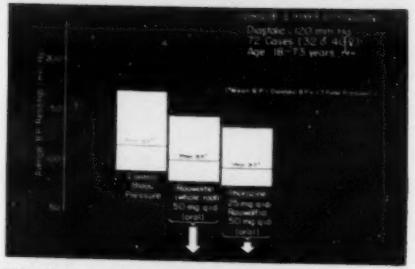
Fig. 13.—Side-effects of hydralazine. Headache; nervous depression; "lupus"; "rheumatoid arthritis."

Fig. 14.—Side-effects of Rauwolfia serpentina. Nasal stuffiness; sedation; bradycardia and diarrhea.

Fig. 15.—Side-effects of chlorpromazine. Sedation; obstructive jaundice (none in this series of 350 cases).

Grade 1

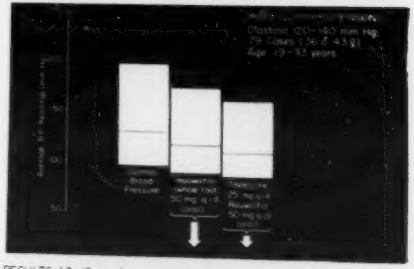
%	Rauwolfia (whole root) (50mg q.i.d.)	Thorazine (25 mg q.i.d.) + Rauwolfia (50 mg q.i.d.)
Becoming Normotensive	81	95
Cardiac Hypertrophy Decreased	72	95
Renal Function Improved	15	48
Fundus Improvement	60	80
Subjective Improvement	65	94
Side Effects	13	1
Toxicity	0	0


Diastolic 120 mm Hg
72 Cases (32 ♂ 40 ♀)
Age 18-73 years
Blood Pressure
Rauwolfia (whole root) 50 mg q.i.d. (oral)
Thorazine 25 mg q.i.d. Rauwolfia 50 mg q.i.d. (oral)

RESULTS (2-18 mos.)
% Cases becoming Normotensive 81% 95%

Grade 2

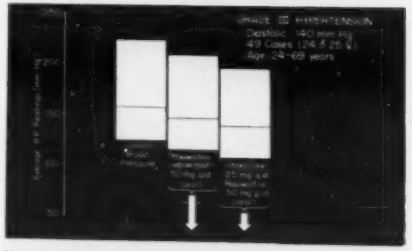
%	Rauwolfia (whole root) (50 mg q.i.d.)	Thorazine (25 mg. q.i.d.) + Rauwolfia (50 mg q.i.d.)
Becoming Normotensive	21	51
Cardiac Hypertrophy Decreased	90	94
Renal Function Improved	11	58
Fundus Improvement	2	54
Subjective Improvement	60	98
Side Effects	15	0
Toxicity	0	0


Diastolic (120-140 mm Hg)
74 Cases (36 ♂ 43 ♀)
Age 19-53 years
Blood Pressure
Rauwolfia (whole root) 50 mg q.i.d. (oral)
Thorazine 25 mg q.i.d. Rauwolfia 50 mg q.i.d. (oral)

RESULTS (2-18 mos.)
% Cases becoming Normotensive 21% 51%

Grade 3

%	Rauwolfia (whole root) (50 mg q.i.d.)	Thorazine (25 mg q.i.d.) + Rauwolfia (50 mg q.i.d.)
Cases Attaining Mean B.P. < 130	14	31
Cardiac Hypertrophy Decreased	90	96
Renal Function Improved	2	64
Fundus Improvement	0	62
Subjective Improvement	40	94
Side Effects	20	1
Toxicity	0	0


Diastolic 140 mm Hg
49 Cases (24 ♂ 25 ♀)
Age 24-69 years
Blood Pressure
Rauwolfia (whole root) 50 mg q.i.d. (oral)
Thorazine 25 mg q.i.d. Rauwolfia 50 mg q.i.d. (oral)

RESULTS (2-18 mos.)
% Cases attaining Mean B.P. < 130 mm. 14% 31%

News and Comment

ANNOUNCEMENTS

Pediatric Refresher Courses.—The following short refresher courses will be given at the Children's Hospital of Philadelphia in May and June, 1957.

1. PEDIATRIC ADVANCES FOR PEDIATRICIANS AND GENERAL PRACTITIONERS. May 27-31, 1957. Conducted by the Staff of the Children's Hospital of Philadelphia, in collaboration with the Department of Pediatrics of the University of Pennsylvania and the Staff of the Camden Municipal Hospital. Tuition, $110.

2. PRACTICAL PEDIATRIC HEMATOLOGY. June 3, 4, and 5. Conducted by Irving J. Wolman, M.D., and other members of the Hematology Department of the Children's Hospital, under the auspices of the Graduate School of Medicine, University of Pennsylvania. Tuition, $75.

3. BLOOD GROUP INCOMPATIBILITIES AND ERYTHROBLASTOSIS FETALIS. June 6 and 7. Conducted by Neva Abelson, M.D., and Thomas R. Boggs Jr., M.D., of the Philadelphia Serum Exchange of the Children's Hospital of Philadelphia, under the auspices of the Graduate School of Medicine, University of Pennsylvania. Tuition, $50.

Inquiries should be addressed to Irving J. Wolman, M.D., Children's Hospital of Philadelphia, 1740 Bainbridge St., Philadelphia 46.

Books

EDITED BY WILLIAM B. BEAN, M. D.

BOOK REVIEWS

Clinical Toxicology. Ed. 3. By C. H. Thienes, M.D., Ph.D., and T. J. Haley, Ph.D. Price $6.50. Pp. 457. Lea & Febiger, 600 Washington Sq., Philadelphia 6, 1955.

As stated in the authors' preface, "This book is written as a classroom text and as a guide for the general practitioner." As such it is not an advanced treatise on toxicology, but rather an easily readable book from which anyone with a basic medical education can rapidly assimilate fundamental data on the drugs causing a similar symptom-complex.

Because of the brevity of the book and its organization into sections, each dealing with a symptom-complex, it serves as a rapid means of differential diagnosis. It should be of distinct help to any practitioner under the pressure of an emergency. In fact, I would heartily recommend its presence in every emergency room for ready reference.

The authors have drawn information from many medical disciplines. With slight variation each drug is discussed under the following topics: toxic dose; source and chemistry; etiology of poisoning; symptoms and actions; duration of poisoning; fate and excretion; pathology; diagnosis; cause of death, and treatment. Because of the scope of the book many available data were omitted. The greatest criticism of the book is its complete lack of references.

The last part of the book (158 pages) is devoted to the "Chemical Diagnosis of Poisoning." This section is inadequate for the toxicologic chemist, but is of some value to the clinician. It describes many simple tests which might be performed by inexperienced persons to serve as presumptive evidence. This section should also be quit adequate for an introductory course in toxicology.

Despite the recent publication date, there are no data on many of the newer drugs, such as the antihypertensive and tranquilizing drugs, both of which are potential poisons. One should recognize that this is an evil inherent in the necessary delay between completion of the manuscript and publication.

The book would benefit by strengthening in three areas. The sections on pathology are quite limited. Since so many drugs produce death by anoxia, a chapter dealing with the pathology of anoxia would be preferable to the repeated but brief references to anoxic changes. Finally, the significance of assay results either before or after death is quite variable depending on the nature, excretion, and time after ingestion of the drugs. Information on this problem is quite sketchy, but its compilation here would be of decided value.

Within its limitations, namely, a rapid reference and an introductory text, this book should serve its purpose well.

J. M. B. BLOODWORTH JR., M.D.

Low-Fat Cookery. By Evelyn S. Stead and Gloria K. Warren. Price $3.95. Pp. 184. McGraw-Hill Book Company, Inc., 330 West 42d St., New York 36, 1956.

Mrs. Stead and Mrs. Warren offer menus and methods of cooking designed to reduce the total daily fat intake from the customary 100 gm. of the average American diet to 25 or 50 gm. They make no discrimination among types of fats, since those most likely to be "related to" atherosclerosis, overweight, and diabetic problems have not been identified. The authors naturally advise avoiding the obvious fats, such as butter, margarine, shortenings, and oils, and include tables showing the fat content of common foods. They suggest mostly carbohydrate substitutes for the "invisible" fats of lean meats, eggs, cheeses, cream, chocolate, soybeans, and nuts.

Recipes are concocted in wise recognition of the fact that people prefer to eat what they like and what they are accumstomed to, rather than what will preserve them to a ripe old age. Mock cream sauces and cheese dips, lardless pie crust, butterless cakes, and skimmed milk custards are designed to imitate the appearance and flavor of the dangerous originals. In most cases they sound rather successful, particularly the desserts and sauces, but many a

cook might hesitate over the cornstarch and pectin salad dressings! The fatless cooking techniques, particularly for meats, should be as useful as they are ingenious.

It is apparent that the adjustments of diet must be made largely by the cook and require little self-denial on the part of the consumer, provided he eats at home. Abroad he must grow up and face the fats.

ABIGAIL S. BEAN

EDITOR'S NOTE.—If professors' wives can write cookbooks, professors' wives can also write reviews of them. In the self-selection of foods, adults, and children for that matter, may act as wanton gluttons, so that the prevailing form of malnutrition in this country today is obesity. The question posed by this cookbook is whether we can have our cake and eat it too. We (my wife as cook and the children and I as willing test subjects) have tried a number of the recipes and found some excellent and many tolerable; but others yielded results resembling a combination of sand and billboard paste. My reaction is to blame the authors, not the cook. No doubt this does have the effect of reducing Calorie intake, which, after all, seems to be the most important therapy needed in the country today. The resemblance which one or two of the products built according to the specifications of this cookbook bear to food was summed up years ago by Bobby Jones when someone greatly enlarged the holes in golf greens to ease the pangs of that game—"very interesting but not golf."

WILLIAM B. BEAN, M.D.

Ciba Foundation Symposium on Bone Structure and Metabolism. Edited by G. E. W. Wolstenholme and Cecilia M. O'Connor. Price, $8. Pp. 299, with 121 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1956.

This little volume brings together the ideas and investigations of a number of eminent authorities in the field of bone structure and metabolism. The subject matter varies from basic biochemical and physiologic information to the latest in clinical investigation. The individual reports are concise, highly readable, and well illustarted. Because of personal interests, I was particularly impressed by the topics on metabolic studies of vitamin D, the mode of action of vitamin D, variations in sensitivity to vitamin D, present knowledge of parathyroid function, and observations on experimental bone disease. Undoubtedly a number of the other topics would appeal more to other readers, for this book brings together a wealth of information for the student of bone disease and metabolism of calcium and phosphorous. This book would be highly useful for persons with a special interest in this field but probably would not appeal greatly to the general practitioner or to the beginning student.

ROBERT E. HODGES, M.D.

Health and Demography. U. S. Department of Health, Education, and Welfare. Prepared by Halbert L. Dunn, M.D. Price, not given. Pp. 94, with illustrations. U. S. Government Printing Office, Washington, D. C., 1956.

For anyone who wants to get a quick birds'-eye view of the trends of disease of the regions of increased population and of the shifts in age of the densities and directions of migration into and out of various states, this book presents material in immediately accessible form. It highlights the real revolutions which have occurred in life expectancy within the memory of living man in public health and in the attitudes of persons toward disease, health, doctors, medicine, and science. Dr. Dunn, who gathered this material together, has made many contributions, not only in the field of medical and public health statistics, but as a provocative thinker, writer, and essayist whose ideas range wide and who has been a sharp but far-seeing critic of our society and our civilization. While this book contains the background for a fairly pessimistic view of man's ability to handle his own affairs, at least it is presented objectively and as a timely warning for those who, by their wisdom and power, might influence for the better certain unhappy trends in contemporary society.

WILLIAM B. BEAN, M.D.

Annual Review of Physiology. Vol. 18. Edited by Victor E. Hall. Price, $7. Pp. 591. Annual Reviews, Inc., Stanford, Calif., 1956.

Reviewing a review hardly permits a precise evaluation of merit or allows for introspective interpretation. However, there is no question that this, the eighteenth of an important and vital series of volumes, continues to maintain the high level attained

by its predecessors. This book is of utmost value to all physicians permitting them to observe the tremendous advances being made in physiology and to note that there is rapid application of this knowledge to medical practice. This is not a volume that can be read in one's spare moments. For those who would appreciate a short synopsis of physiological advances, it might be a worthwhile addition to these volumes if the editors required a summarization at the end of each section.

STEVEN M. HORVATH

Year Book of Pathology and Clinical Pathology (1955-1956 Year Book Series). Edited by William B. Wartman, M.D. Price, $6.50. Pp. 480, with 161 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1956.

This year book continues to be one of the best in this very important series. The fact that it has a personality is a reflection of the skill of its editor, Dr. Wartman, and of the abstractors who have done a splendid job of condensing complex subjects to the state where the average medical reader can understand enough to want to go back to the original article, which after all is the main purpose of such books. Spritely editorial comments are sprinkled throughout. One of them in a single sentence may shift the orientation or clinch the argument. The reproduction of numerous illustrations adds conspicuously to the value of the book, and the use of brief critical or analytical essays, which some of the other year books in this group do not have yet, has added to the quality and style of the work.

WILLIAM B. BEAN, M.D.

Lectures on the Scientific Basis of Medicine. Vol. IV: 1954-55. Edited by British Postgraduate Medical Federation. Price, 37 s. 6 d., $6.50. Pp. 397, with illustrations. Athlone Press, University of London, 2 Gower St., London, W. C. 1, 1956.

Conscientious physicians who are haunted by the lost battle of keeping up with "the medical literature" from time to time may get solace from reading such essays as are contained in this volume. Most of them will be perfectly intelligible to physicians, and a good many could be understood by the well-educated layman. They give a survey of what is going on and a recapitulation of current work in diverse fields of modern science. Even for those in esoteric corners of biology and medicine, the writers have managed to present abstruse material in a way which is not just understandable but a pleasure to read. The essays run the gamut from "Why Biophysics?," by A. V. Hill, to "Histochemistry and its Application to the Basic Sciences," by Pearse. Among the remarkable and delightful pieces of information, one may glean an example from Sir Victor Negus—the fact the muscles which rotate the arytenoid cartilage in man are strikingly similar to those of the lioness and rather different from those of the alligator. This comforting information is no less elegantly displayed than the vivid picture of sulfated mucin in the foregut of the Eastern fence swift lizard (Sceloporus undelatus). There is a large store of interesting facts about science, salted down with common sense and wisdom. All in all, these lectures and their elegant reproduction might serve as a model for us to emulate in this country.

WILLIAM B. BEAN, M.D.

Venous Return. By Dr. Gayard A. Brecher. Price, $6.75. Pp. 148, with 55 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1956.

This small monograph on "Venous Return" is an interesting discussion of some aspects of the functions of veins. It is an important book because the venous circulation is so frequently ignored and has received relatively little study. Dr. Brecher's own contributions to the problem of the venous circulation, as well as the literature and ideas obtained from other investigators and their publications, are reviewed. Many of the illustrations can be found in essentially the same form in other publications, but their repetition here is advisable because some of the simplest ideas in hemodynamic phenomena are not adequately considered by undergraduate and postgraduate students in the field of medicine.

The book contains aspects of venous physiology which need to be clarified, and certain phases of the unknown have resulted in some inconsistencies and possibly highly controversial statements in Brecher's book. For example, on page twenty-eight it is stated, "Thus it is up to the reports of the opposite view to furnish indisputable

experimental evidence that blood is actively sucked into the ventricles at the beginning of diastole." The author then refers to the footnote on page ten, in which he states that he himself has produced evidence that the left ventricle sucks blood. He should have noted that the studies of Wiggers have been interpreted previously to show that the ventricles do suck blood. The quantity of blood sucked and the importance of this suction are yet to be determined.

There is a tendency for the author not to differentiate clearly between linear rates of flow and volume rates of flow. These can have considerable hemodynamic significance, of course, and whereas the author is aware of this, it might be confusing at times for the reader.

One phase of the discussions that is given inadequate consideration by the author is that concerned with variations in smooth muscle tone within the walls of the veins. Venous tone varies from time to time and is certainly influenced by humoral factors, organic nervous system activity, and, in experimental and clinical medicine, by drugs. For example, in the discussion of mitral stenosis, tricuspid stenosis, and pericardial effusion, no consideration is given to the possible role of the sympathetic nervous system and active smooth muscle contraction in the control of venous pressure and venous return. The innervation of the veins, the fact that veins have been shown to respond to vasomotor phenomena, either chemical, physical, or nervous in origin, would certainly lead one to believe that they should not be considered as passive tubes under the influence of such factors as skeletal muscle pumps or the central cardiac pump, but as being actively influenced by their own smooth muscle.

Except for an occasional problem of this sort, the monograph is a good one. The author makes poignant points of the problem of partial and complete venous collapse and its influence on pressure gradients and the rates of volume flow through the venous system. Obviously, a book of only one hundred twenty-seven pages on a subject so vast as venous return can only cover certain selected phases of the problem. Those that have been presented are of interest, and the book is recommended to anyone who is interested in veins. It should be remembered, however, that some of the discussions represent the opinion of the author, and his interpretation of venous phenomena and are not necessarily the opinion of other investigators in the field.

GEORGE BURCH, M.D.

Handbook of Pediatric Medical Emergencies. By Adolph George De Sanctis and Charles Varga. Price, $6.25. Pp. 389, with 73 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1956.

This is an inexpensive book which would be particularly useful to the busy practitioner who does not have immediate access to adequate library facilities when faced with a medical emergency. It contains a great deal of information pertaining to the diagnosis as well as the treatment of various situations of acute illness in infants and children. Doses of antibiotics and numerous medications for pediatric patients are adequately discussed. The subject material covers a wide span of emergencies, including the cardiovascular, genitourinary, nervous, and respiratory systems. Numerous other problems which commonly confront physicians are reviewed, such as poisonings, epistaxis, and insect, animal, and human bites. A chapter describing techniques of a number of procedures essential in pediatric care, such as venapunctures, aspiration of subdural hematoma, and paracenteses, is made quite lucid by photographs and diagrams. At the conclusion of each chapter a list of recommended references is presented where the reader may obtain further details concerning the subjects outlined. Relatively superficial and occasionally dogmatic consideration is inevitable in any book such as this, written in outline form. However, the authors have accomplished in admirable fashion their primary intent—a readily available compact source of information concerning the diagnosis and treatment of medical emergencies in children.

GEORGE R. BARNES JR., M.D.

Etiologic Factors in Renal Lithiasis. Edited by Arthur J. Butt. Price, $12.50. Pp. 401, with 165 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

In this volume the editor has called upon an impressive group of authors to present, from numerous aspects, the available information concerning kidney stones. The his-

torical review is fascinating and well done. Metabolic factors are discussed under a variety of headings and in numerous diseases. These include abnormalities of calcium, phosphorous, oxalate, uric acid, and amino acid metabolism. There are also detailed discussions of sulfonamide concretions and the relationship of urinary calculi to stasis, obstruction, and infection. Additional factors are considered in the etiology, including geographical locations, race, climate, and water supply. The remainder of this book is compiled in such a fashion as to support a theory previously advanced by the editor, Dr. Butt. These topics are fascinating and well presented but not entirely convincing. Thus the reader is led gently through discussions of urinary colloids, mucopolysaccharides of the kidney, ground substances, and the effect of hyaluronidase on human urine. Finally the climax is reached with presentation of Dr. Butt's ideas on renal lithiasis and the effects of hyaluronidase in prophylaxis and therapy of this condition. A final chapter on analysis of calculi completes the volume.

There can be no doubt that the greater part of this book is useful. The ideas presented by Dr. Butt remain controversial in the minds of many clinicians.

ROBERT E. HODGES, M.D.

Basic Physiology of Exercise. By Fred John Lipovetz. Price, not given. Pp. 170, with 66 illustrations. Burgess Publishing Company, 426 S. 6th St., Minneapolis 15, 1954.

This book is a strange compilation of fact and fiction inadequately digested and similarly regurgitated. If such material is being presented to our college students as exemplifying a branch of science, it is no wonder that these young people enter other fields in order to satisfy their intellectual curosity.

STEVEN M. HORVATH

Quantitative Clinical Chemistry. Volume II. Methods. By John P. Peters, M.D., M.A., and Donald D. Van Slyke, Ph.D., Sc.D. Price, $10. Pp. 981, with 99 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1932 (reprinted 1943, 1956).

Peters and Van Slyke first published their monumental work on the quantitative analysis of biological materials in 1932. Except for a few minor revisions made when the book was reprinted for the Army, in 1943, this printing is unchanged. This volume (Volume II. Methods) is almost exclusively devoted to operation and technique of the analytical laboratory. There is a chapter on general chemical techniques as well as a chapter which presents the many special techniques which have been evolved to adapt quantitative analysis to biological fluids. The material in these chapters has stood well the test of time. Although many analytical procedures have been adapted for reading on the spectrophotometer, a perusal of this book, published twenty-five years ago, demonstrates graphically how little basic analytical techniques have changed over the last quarter of a century. This book is of value to the career investigator because of the presentation of many techniques long since discarded by the routine hospital laboratory but still of frequent value as research procedures.

J. M. B. BLOODWORTH JR., M.D.

Perspectives in Physiology. Edited by Ilza Veith. Price, $3. Pp. 171, with 16 illustrations. American Physiological Society, 9650 Wisconsin Ave., Washington 14, D. C., 1954.

For anyone interested in medical education in this country and abroad, the excellent essays contained in "Perspectives in Physiology" should give grounds for serious thought. This book documents clearly and in a personal way the many different relationships to physiology to medicine and biology, how the problems vary from country to country, and the wide range of efforts at solutions of such problems as exist. Reduced to the simplest terms, scientists, teachers, and scholars in physiology are not reproducing themselves fast enough to keep up with the increasing demand and scope of their discipline. The basic reason is a financial one and is of grave concern to all those interested in medical education who can see the writing on the wall. The failure of the basic sciences to improve their financial situation will mean an inevitable decline in the quality of medical schools and students and ultimately can lead only to a decline in the practice of medicine. Another aspect of the problem much more important in this country than abroad in British and Continental countries is the relatively poor status of the scholar, the faint derision attached to the title "professor," and the crude misinterpretation of democracy as a guarantee that everyone is as good as everyone else

whether they are or not. The deification of the athlete and entertainer is the obverse of the coin of the suspicion of eggheads in particular and of the use of intelligence in general. This thoughtful little volume will be of interest to historians now and in the future, for the answers to the questions skilfully and thoughtfully posed in this book are obscure at the moment. Providing the proper solution is vital in the days ahead if we are to continue to advance in medicine and in science.

WILLIAM B. BEAN, M.D.

Clinical Laboratory Diagnosis. Fifth Edition. By Samuel A. Levinson and Robert P. MacFate. Price, $12.50. Pp. 1246, with 244 illustrations, 13 plates, and 142 tables. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1956.

The fifth edition of this familiar laboratory and clinical reference book is a handsomely bound volume which maintains the format used in the preceding volumes. It is divided into twenty chapters and an appendix, each chapter being listed in outline form for rapid location of those procedures which one may wish to refer to at a moment's notice. The authors have done an admirable job of incorporating worthwhile advances in the field of laboratory diagnosis into this volume while at the same time omitting procedures which are not as yet of proved value or which offer little advantage over well-established methods. One particularly laudable feature of this new volume is the incorporation of pediatric hematologic techniques under the general topic of hematology, thus reuniting the fields of pediatrics and medicine.

The authors have achieved excellence in the preparation and execution of this laboratory book. It will serve students and practitioners alike and will continue to find wide acceptance in clinical laboratories. One regretable but perhaps unavoidable defect is the paucity of bibliography. No doubt this was necessitated by the economics of publication. Nonetheless, it is a book to be highly recommended.

ROBERT E. HODGES, M.D.

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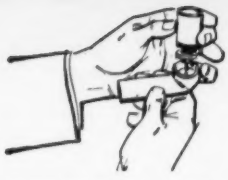

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Lemere, F.: Northwest Med. **54**: *1098, 1955.*

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Sokoloff, O. J.: A.M.A. Arch. Dermat. **74**: *393, 1956.*

3 "Of special importance is the fact that Miltown does not appear to affect autonomic balance—which in alcoholics is often unstable . . ."

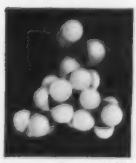
Thimann, J. and Gauthier, J.W.: Quart. J. Stud. Alcohol. **17**: *19, 1956.*

4 "The [relative] absence of toxicity, both subjectively and objectively, is an important feature in favor of Miltown. In addition, there were no withdrawal phenomena noted on cessation of therapy, whether it was withdrawn rapidly or slowly."

Borrus, J.C.: J.A.M.A. **157**: *1596, 1955.*

5 "Miltown is of most value in the so-called anxiety neurosis syndrome, especially when the primary symptom is tension . . . Miltown is an effective dormifacient and appears to have . . . advantages over the conventional sedatives except in psychotic patients. It relaxes the patient for natural sleep rather than forcing sleep."

Selling, L.S.: J.A.M.A. **157**: *1594, 1955.*



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3 or 4 times daily.

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* Smith, J. A.: *J.A.M.A.*, 152:384, May 30, 1953. Brown, W. T. and Smith, J. A.: *South. Med. Jour.*, 46:582, June, 1953. Smith, J. A.: *Postgrad. Med.*, 16:316, Oct., 1954. McCullagh, W. H.: *Jour. Florida Med. Assn.*, 41:718, Mar., 1955.

Mebaral (brand of mephobarbital), trademark reg. U. S. Pat. Off.

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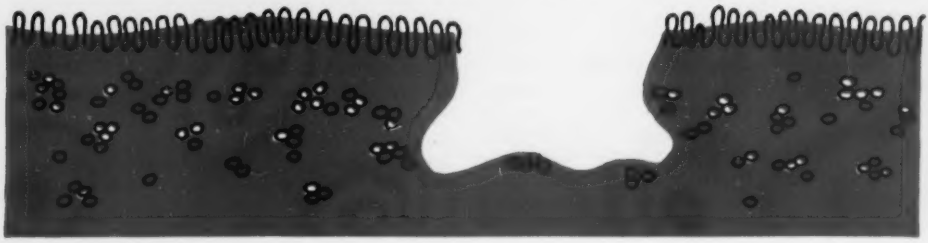

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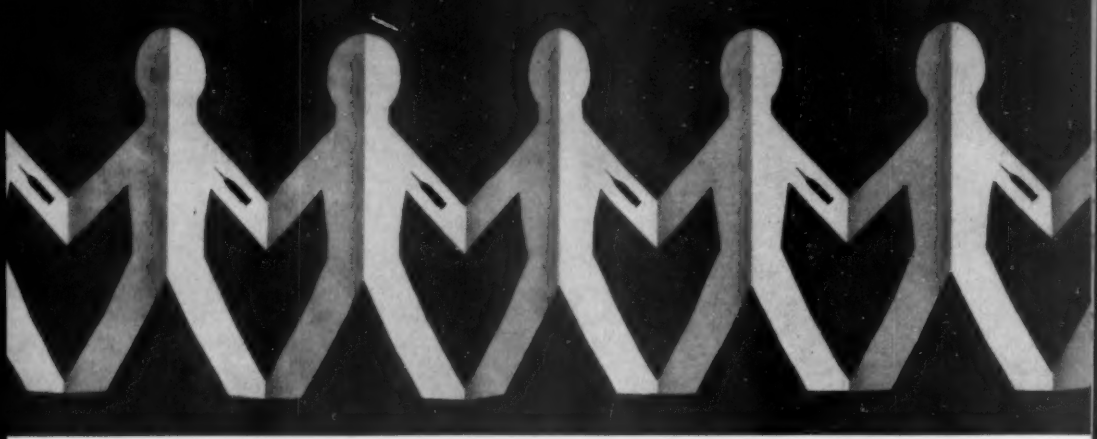

which donor would you consider "normal"?

A problem of particular significance in the regulation of anticoagulant dosage is this: staff physicians interpret prothrombin times and adjust therapy against the "normal." However, errors in evaluation are frequently caused by differences in the clotting mechanism of so-called "normal" donors. Even pooled plasma is subject to variation, particularly because accessory clotting factors deteriorate when stored only a few hours. Diagnostic Plasma Warner-Chilcott, however, is precisely standardized for coagulation factors, assuring reproducible clotting behavior and reliable normal readings.

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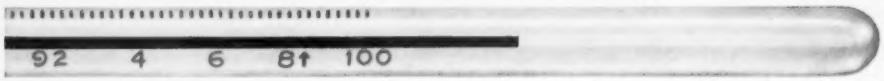

doctor?

Naturally not. Missing calibration makes it worthless.

Equally useless and dangerous is a "quantitative" urine-sugar test that does not quantitate dependably, or omits readings in the critical range.

Enzyme urine-sugar tests are sensitive and specific for glucose—excellent "yes" or "no" tests but undependable for quantitation. King and Hainline,[1] after testing 1,000 urines, found an enzymatic urine-sugar test unable to distinguish in the important range between ½ per cent and 2 per cent or more of urinary glucose. Leonards,[2] in a report on 4,020 tests, revealed that "...in 502 out of 804 tests the wrong interpretation was made." He concluded that enzymatic urine-sugar testing "...as a quantitative procedure is unsatisfactory and can lead to serious error in the interpretation of a patient's clinical condition."[2]

Failure to recognize this limitation of enzyme tests may result in incorrect insulin dosage,[2] and may lead to diabetic complications.

(1) King, J. W., and Hainline, A., Jr.: Commercial Glucose Oxidase Preparations for the Detection of Glucose in Urine, Cleveland Clin. Quart. **23**:212, 1956. (2) Leonards, J. R.: Evaluation of Enzyme Tests for Urinary Glucose, J.A.M.A. **163**:260 (Jan. 26) 1957.

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